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Final Report

ADVISORY COMMITTEE ON HUMAN RADIATION EXPERIMENTS

Supplemental Volume 1

Ancillary Materials

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An Internet site containing ACHRE information (replicating the Advisory Committee's original gopher) will be available at George Washington University. The site contains complete records of Advisory Committee actions as approved; complete descriptions of the primary research materials discovered and analyzed; complete descriptions of the print and non-print secondary resources used by the Advisory Committee; a copy of the Interim Report of October 21, 1994; a copy of the Executive Summary and Guide to Final Report; and other information. The address is http://www.seas.gwu.edu/nsarchive/radiation. The site will be maintained by the National Security Archive at GWU.

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ADVISORY COMMITTEE ON HUMAN RADIATION EXPERIMENTS
1726 M STREET, N.W., SUITE 600
WASHINGTON, D.C. 20036

October 1995

To the Members of the Human Radiation Interagency Working Group:

Secretary Hazel O'Leary, Department of Energy
Secretary William Perry, Department of Defense
Attorney General Janet Reno, Department of Justice
Secretary Donna Shalala, Department of Health and Human Services
Secretary Jesse Brown, Department of Veterans Affairs
Director Alice Rivlin, Office of Management and Budget
Director John Deutch, Central Intelligence Agency
Administrator Daniel Goldin, National Aeronautics and Space Administration

On behalf of the Advisory Committee on Human Radiation Experiments, it is my privilege to transmit to you our Final Report.

Since the Committee's first meeting in April 1994 we have been able to conduct an intensive inquiry into the history of government-sponsored human radiation experiments and intentional environmental releases of radiation that occurred between 1944 and 1974. We have studied the ethical standards of that time and of today and have developed a moral framework for evaluating these experiments. Finally, we have examined the extent to which current policies and practices appear to protect the rights and interests of today's human subjects. This report documents our findings and makes recommendations for your consideration.

The committee listened to the testimony of more than 200 public witnesses who appeared before us. We are deeply grateful to all these witnesses, who overcame the obstacles of geography and emotions to assist us.

Our work and this report would not have been possible without the extraordinary effort the President and you put forward to open the government's records to our inquiry and thus to the nation. We are especially pleased that, through our joint efforts, the American people now have access to the tens of thousands of documents that bear on this important history.

None of our conclusions came easily. We endeavored, both as individuals and as a committee, to live up to the responsibility with which we were entrusted. This report represents the consensus of fair-minded people who gave the best they had to offer to their fellow citizens.

We thank President Clinton for this opportunity and for his courage and leadership in appointing the Advisory Committee.

Ruth R. Faden
Chair, Advisory Committee
on Human Radiation Experiments

Advisory Committee on Human Radiation Experiments

Advisory Committee on Human Radiation Experiments

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DOCUMENTARY NOTE

The otherwise unpublished documents referenced in this volume are identified by their places in the ACHRE Research Document Collection. These identifiers, or *ACHRE document numbers*, have four parts: originating institution, date of receipt, order of receipt, and document number. For example, DOE-051094-A-123 is the 123d document described in the first ("A") Department of Energy ("DOE") shipment (or *accession*) received on May 10, 1994 ("051094"). One of the appendices found in the Final Report of the Advisory Committee on Human Radiation Experiments, *A Citizen's Guide to the Nation's Archives*, provides instructions for using references to the ACHRE collection to find documents there and in the collections of the National Archives and at the agencies.

SUPPLEMENTAL VOLUME 1

ANCILLARY MATERIALS

1

DOCUMENTS PERTAINING TO AGENCY ETHICS POLICIES

The Advisory Committee collected a large number of documents pertaining to the origins and development of the policies regarding human subjects research sponsored or performed by the U.S. government. We were able to draw upon previous scholarship on the laws, policies, and practices in the period from 1944 to 1974, but we also discovered a great deal of new information from federal records collections, some of which had been classified until recently. Although the entire body of information assembled by the Advisory Committee will be available at the National Archives, we felt that it would be worthwhile to publish as many of these new documents as possible to make them more readily accessible to scholars and the general public.

The documents included in this chapter have been arranged in chronological order. We have also provided the citation for each document as it appears in the endnotes of our final report. All of the reprinted documents were cited within part I of the final report. Not all of the documents from part I are included in this chapter for two major reasons: (1) we were not able to obtain copyright permission for some documents that we received from nongovernmental institutions and individuals; and (2) some of the documents, through many generations of photocopying, are difficult to read and would be illegible in this format. As mentioned above, all of the documents will be available to the public in the Advisory Committee's materials stored at the National Archives.

Supplemental Volume 1

List of Reprinted Original Documents
on History of Agency Ethics, Policies and Practices

Supplemental Volume 1

Supplemental Volume 1

Supplemental Volume 1

Supplemental Volume 1

History of the

RESEARCH DIVISION

Bureau of Medicine and Surgery

U. S. Department of the Navy

by

Charles W. Shilling

Captain, Medical Corps, U. S. Navy, Retired

Particularly pleasing to a research minded individual was the sp endorsement of the request for a research laboratory at the new Naval ical School prepared by CDR C. S. Stephenson, MC, USN:[9] "No record has been found of an institution, anywhere, in the million dollar class which does not have a well organized program of research. Yet the Medical Department of the Navy spends over four million dollars a year for supplies and equipment and has no functioning research program. True, we have had sporadic fits of research, but none have fulfilled the meaning of the word, and in the main have died of nonsupport, lack of appreciation of the value of the research, or purely to carry out the habit spasm policy of rotating personnel. Compared with industrial research as it is conducted by the great electrical and chemical foundations, all medical research is most haphazard, individualistic, and, hence, not highly efficient". BUMED needs many more Stephensons!

Experimentation with human subjects, and the question of informed consent was much in the medical and lay press in 1974, but nine years before the Research Division was formed, such experimentation was agreed upon for physiological research with the submarine escape device, the "lung", and in deepsea diving activity conducted at the EDU at the Navy Yard, Washington, D.C. In 1932 BUMED wrote to the SecNav, giving in detail the protocol for the planned experiments and requesting approval.[10] SecNav approved the request for the work, with the understanding that all subjects should be informed volunteers; that the detailed protocol be approved in advance, and that every precaution be taken to prevent accidents. It should be noted that the work was entirely supported by the Bureau of Construction and Repa (BuC&R) but that BUMED had at least one medical officer assigned with priate assistants, and that there was an advisory committee with a BUM representative on it, in the early days, CAPT E. W. Brown, MC, USN.

But permission for animal experimentation was not so easy. The author will be forgiven, I trust, for augmenting the formal history gleaned from the cold official letters and formal reports by adding a personal experience. We had been doing an extensive biochemical experiment on dogs breathing oxygen under pressure in the chamber at EDU, attended by air breathing medical personnel, and were quite well along when Irene Castle came to Washington and made an emotional plea before a committee of Congress to stop all animal experimentation in the U. S. This antivivisectionist tirade frightened the Chief, BuC&R, who ordered our work discontinued. Knowing that the months of hard and dangerous work under high pressure were about to be lost, and

[9]Memorandum NC43/S-E(25)CO/elh dated 9 December 1939 to Chief, BUMED. Subject: Research laboratory for the new NMS, signed by W. Chambers and enclosing a statement by LT A. R. Behnke, Jr., MC, USN, proposing the laboratory.

[10]BuM&S letter of 5 April 1932, S92(041) to SecNav via BuNav with CNO, Subject: Hazards to personnel in physiological research with submarine "lung" and in deepsea diving at EDU.

b. Dogs, cats, and other animal pets kept on military reservations will be vaccinated against rabies when in the opinion of the surgeon such immunization is indicated.

c. When a case of rabies occurs in an animal at a military station, all dogs and cats at such station will be restricted as recommended by the surgeon.

d. Any animal that has bitten a person, and any animal suspected of being rabid, will be kept in confinement under the observation of a veterinary officer, if such officer is available, otherwise the surgeon, for a period of at least 2 weeks, or until definite symptoms of rabies develop. If such symptoms do not develop in this period, the animal may be considered free from the disease and be released. If suspicious symptoms develop, the animal should be permitted to live until definite symptoms of rabies are present or death occurs. The animal will then be decapitated and the head and neck forwarded to the service command laboratory for examination as prescribed in AR 40-310 and in current Technical Manuals. In no instance will an animal be destroyed by shooting through the head, as this procedure interferes with laboratory tests for rabies. Any animal that has been bitten by another animal, known, or reasonably suspected to be rabid, will be immediately destroyed or confined under observation for a period of 120 days, at the end of which period it may be released if no symptoms of rabies have developed.

(3) Any person bitten by an animal may be vaccinated against rabies when in the opinion of the surgeon such action is indicated.

36. Scabies (itch).—*a.* Regulations pertaining to bathing and personal hygiene will be enforced at all times. See AR 40-205.

b. Cases will be segregated and treated as recommended by the surgeon.

c. The bedding and clothing of all cases will be disinfested as prescribed in AR 40-205.

37. Schistosomiasis.—In known endemic areas all personnel will be instructed concerning methods of infection and warned against the danger of wading, swimming, bathing, or otherwise exposing the skin to infested water.

38. Tetanus (lockjaw).—All military personnel on active duty will be immunized against tetanus as prescribed in section III.

39. Trachoma.—In regions where trachoma is common, personnel will be warned of the danger of infection from direct or indirect contact with infected persons. The danger of using towels in common and of rubbing the eyes with unclean hands will be stressed.

40. Tularemia.—Personnel will be warned of the danger of contracting tularemia by the bites of blood-sucking flies and ticks or the handling of infected game.

41. Yaws (frambesia).—In areas where yaws is prevalent special attention will be given to the control of flies, to the disinfection of minor wounds and abrasions of the skin, and to minimizing contacts between troops and natives.

[A. G. 710 (7-18-41).]

BY ORDER OF THE SECRETARY OF WAR:

G. C. MARSHALL,
Chief of Staff.

OFFICIAL:
J. A. ULIO,
Major General,
The Adjutant General.

DISTRIBUTION:
A; E.

U. S. GOVERNMENT PRINTING OFFICE 1941

Superseded 40-210 9-15-41

ARMY REGULATIONS, No. 40-210 } WAR DEPARTMENT, WASHINGTON, April 21, 1925.

MEDICAL DEPARTMENT.

THE PREVENTION OF THE COMMUNICABLE DISEASES OF MAN—GENERAL.

1. General provisions.—*a. Objects of sanitary science.*—The main objects of sanitary science are—

(1) To determine the causes of communicable diseases.

(2) To discover the methods by which pathogenic organisms are transmitted to man.

(3) To apply effective measures for eradicating or controlling the causes and for preventing the transmission of infections to others.

b. Influence of disease rates on military campaigns.—Military operations have not infrequently been seriously interfered with in former times by communicable diseases, but during recent wars the deaths from battle casualties have exceeded deaths from disease in well-disciplined military forces which applied modern methods of disease prevention. When effective sanitary measures are intelligently applied, communicable diseases may occur sporadically but they will rarely assume epidemic form.

c. Research and investigation.—Research and experimental investigations having in view the discovery of methods for conferring active immunity against many of the communicable diseases are being carried on in the Army and will be adopted for general use when their practical value has been demonstrated conclusively. Commanders of all grades are directed to cooperate with the Medical Department in securing volunteers for experimental inoculation or such other investigations as may have the approval of the War Department.

Additional references.—Other provisions relating to the prevention of communicable diseases of men will be found in AR 40-205, 40-215, 40-220, 40-225, 40-230, 40-235, 40-240, 40-245, and 40-310.

2. Responsibility for initiation and enforcement of preventive measures.—*a. Medical Department.*—The Medical Department is charged with the initiation and supervision of measures for the control and prevention of disease in military personnel and among the inhabitants of occupied territories. The functions of officers of the Medical Department are, in the main, of an inspectorial and advisory nature.

b. Commanding officers.—Commanders of all grades are charged with the responsibility of putting into effect the provisions of [illegible] regulations. Many of the regulations relating to hygiene and sanitation [illegible] are prescribed

for the purpose of preventing the spread of communicable diseases, and commanders of all grades will devote attention to the enforcement of these regulations, especially those enumerated below:

(1) The thorough washing of hands after visiting latrines and before each meal.
(2) The proper sterilization of dishes and mess kits.
(3) Vaccination against smallpox, typhoid and the paratyphoid fevers.
(4) The prevention of venereal disease.
(5) The proper ventilation of barracks.
(6) The elimination of overcrowding.
(7) The eradication of mosquitoes.
(8) The destruction of flies, lice, and other insects.
(9) The purification of nonpotable water supplies.
(10) The proper disposal of human excreta and matnpe.
(11) The proper disposal of garbage.

b. The principal objects of military hygiene and sanitation.—a. General.—Certain of the measures enumerated in these regulations relate to the prevention of disease in the individual while others deal directly with the communicable disease itself and place the responsibility for prevention of its spread on specially trained experts.

b. Objects.—A program of military hygiene and sanitation has in view the accomplishment of the following objects:

(1) The continuous maintenance in each individual of the highest possible state of health.
(2) The training of the soldier in such rules of personal conduct as will enable him to avoid the infective agent of communicable diseases.
(3) The specific immunization of each individual against communicable diseases when it is possible of accomplishment.
(4) The supervision of all known infectious cases with a view to preventing the transference of the causative agents to others.
(5) The supervision of the common avenues of transmission with a view to freeing them from any living pathogenic organisms by means of the filtration and chlorination of water, pasteurization of milk, thorough cooking of food, and destruction or exclusion of flies, etc.
(6) The sociological supervision of all infected persons.

c. The scope of preventive measures.—In considering the prevention of communicable diseases it is necessary to have clearly in mind that their prevention or control includes the application of all measures initiated to keep a soldier in the best of health and to improve his physique as well as those procedures that have a direct bearing on prevention. Some of the provisions of regulations relating to military hygiene and sanitation (AR 40-205) have only an indirect bearing on disease prevention, their main purpose being to develop habits of cleanliness, orderliness, and hygienic living in the individual and to create and develop his respect for self. Others have a very direct bearing on disease prevention. The measure of success to be attained in the prevention of communicable diseases is dependent, to a considerable degree, on the efficiency, thoroughness, and intelligence with which all regulations relating both indirectly and directly to disease prevention are carried out. Laboratory and other examinations of specimens are essential for the control of many of these communicable diseases, and the directions for collecting, preparing and shipping specimens are prescribed in AR 40-510.

5. Definition of special terms.—In the application of the regulations relating to the prevention of the communicable diseases of man, the following terms are used as defined below:

a. Contact.—A contact is a person quartered in the same tent, or occupying a near-by bed in a squad room, or closely associated at mess or otherwise with an individual infected with the causative organisms of a communicable disease.

b. Carrier.—The term "carrier," as used in these regulations, is applied to an individual who harbors and excretes pathogenic parasites without showing the usual evidences of the disease produced by the parasite in question. Carriers may be classified as follows:

(1) *True carriers*, who harbor parasites which are pathogenic and virulent. True carriers are subdivided into—
  (a) Incubationary carriers who are temporary carriers in the incubation stage of an infectious disease.
  (b) Convalescent carriers who may be temporary or chronic. Temporary convalescent carriers are persons who are in the convalescent stage of an infectious disease but in whom not as yet eliminated all the causative organisms. Chronic convalescent carriers may have apparently recovered entirely from the disease, but they presumably still have some concealed lesion which permits the parasite to continue its growth; the excretion of parasites in such cases is often intermittent.
  (c) Contact carriers who may be temporary or chronic. Contact carriers are those who acquire parasites from association with cases or carriers without themselves developing the disease.
(2) *Pseudo-carriers*, who harbor organisms morphologically and culturally indistinguishable from pathogenic and virulent parasites which are, however, found on further examination to be nonpathogenic and nonvirulent. During the course of examination these individuals must be regarded as true carriers until nonpathogenicity and nonvirulence are established.

c. Suspect.—A suspect is a person exhibiting signs or symptoms which, though not definitely diagnostic in character, may indicate some stage of a communicable disease.

d. Quarantine.—Quarantine is the application of such restrictive measures to the activities of contacts, carriers, suspects, and cases of communicable diseases as may reasonably be expected to prevent the further spread of the causative organisms of these diseases.

(1) Working quarantine is the segregation of selected carriers or contact groups in such a manner that a given group is not brought in contact with another group or with other persons, yet the performance of certain duties (such as fatigue, drill, instruction, etc.) is not interrupted.
(2) Absolute quarantine is the detention of contacts, carriers, suspects, persons ill with communicable disease, or other groups of individuals, in complete isolation, either individually or collectively, as the circumstances may warrant.

6. Influence of environment.—The specific part that environment plays in the spread of communicable diseases depends upon whether or not it permits of the exchange of human discharges or whether or not certain insects which are known to act as transmitters of disease constitute an integral part of environmental conditions. The presence of certain insects and overcrowding, combined with faulty discipline and limited facilities for bathing the body and washing the hands, contribute to the spread of communicable diseases whenever certain specific infections are introduced into the community. In addition, unfavorable environment will lower body resistance and thereby the individual is predisposed to contract disease. The rapid mobilization of large numbers of recruits and the bringing together of detachments of men from different units for the formation of new organizations result in rapid dissemination of nonpathogenic and pathogenic microorganisms carried by individuals. Such conditions are ideal for the spread of communicable diseases.

7. Principal modes of transmission.—*a. For diseases of the respiratory, intestinal, and urinary tracts.*

(1) Ingestion of pathogenic organisms discharged from the intestinal and urinary tracts with water, milk, and uncooked foods is the principal mode of transmission.

(2) Personal contact is a very important mode of transmission from individual to individual. Infective agents are disseminated directly from the infected person chiefly through discharges from the nose, mouth, bowel, and genito-urinary tract and by direct contact with an infective lesion. An important method of spread is through infectious material on the hands. Sputum and droplets sprayed from the mouth play a significant rôle.

b. Insects.—In certain areas of the United States insects play an important rôle in the transmission of a limited number of diseases (malaria, dengue, etc.). In tropical countries insects are even more important as factors in the spread of the causative organisms of communicable diseases.

8. The establishment of quarantine.—*a. How and when established.*—The establishment of quarantine measures at a military station will be made by the commanding officer, when necessary, upon recommendation of the surgeon. Absolute quarantine of large bodies of troops will be instituted only when a disease of a serious nature exists in a command or threatens to become widely disseminated therein. Ordinarily contacts will be held in working quarantine, and will be subjected to one or more careful physical inspections daily in order that early cases and suspects may be detected. In the control of certain communicable diseases, all quarantine measures may be dispensed with, reliance being placed upon careful physical inspections conducted at intervals to insure detection of cases in their incipiency. The special quarantine measures applicable to the various diseases will be found in the regulations governing the prevention of specific diseases.

b. Section 4792 of Revised Statutes of the United States.—Section 4792, Revised Statutes, which will govern quarantines when applicable, is quoted as follows:

"The quarantines and other restraints established by the health laws of any State, respecting any vessels arriving in, or bound to, any port or district thereof, shall be duly observed by the officers of the customs revenue of the United States, by the masters and crews of the several revenue [illegible] and

by the military officers commanding in any fort or station upon the seacoast and all such officers of the United States shall faithfully aid in the execution of such quarantines and health laws, according to their respective powers and within their respective precincts, and as they shall be directed, from time to time, by the Secretary of the Treasury. * * *"

9. Observation camps for recruits.—Observation camps or barracks for incoming recruits will be established at stations where necessary. Recruits arriving in groups or individually at frequent intervals will be detained in these barracks or camps for observation during a period of time sufficient to insure detection of acute communicable diseases contracted before arrival thereby preventing their introduction into the command. The status of personnel held under observation will ordinarily be that of working quarantine. They will be carefully inspected by a medical officer at least once a day for the detection of disease. The minimum period of observation will be two weeks. In case recruits not known to have been recently exposed to a communicable disease of a serious nature are joining a command at infrequent intervals and in small numbers, they may be assigned directly to organizations provided that they report to the unit surgeon once a day during a period of at least two weeks for examination with a view to detecting acute communicable and other diseases. In large commands receiving great numbers of recruits quarantine camps may be necessary for the segregation of carriers, certain contacts, and suspected cases of communicable diseases.

10. Statistical charts and reports regarding communicable diseases. Surgeons of stations and commands are responsible for the collection, tabulation and graphical presentation of information concerning the incidence of communicable diseases. Tables and charts showing the movement of communicable diseases in commands will be kept available at all times for inspection by commanding officers and inspectors. When rates are in excess of the normal an age every effort will be made to determine and remove the causes.

[A. G. 300.69 (11-1-22).]

BY ORDER OF THE SECRETARY OF WAR:

JOHN J. PERSHING,
General of the Armies,
Chief of Staff.

OFFICIAL:
ROBERT C. DAVIS,
The Adjutant General.

COPY

Letter from J. E. Moore, M. D., to Dr. A. N. Richards October 6, 1942

I have recently received a letter of enquiry from Dr. Charles M. Carpenter of the University of Rochester School of Medicine who believes that he may be able to work out a human experiment on the chemical prophylaxis of gonorrhea. He has asked me to supply him with a statement that in my opinion such human experimentation is desirable. I have in turn replied enquiring from him as to whether he wishes a statement from me on an entirely personal basis or in one of my official capacities - as Chairman of the Subcommittee on Venereal Diseases, National Research Council, or as Special Consultant, U. S. Public Health Service. In either of the latter cases I have pointed out to Dr. Carpenter that I could not make such a statement without the approval of higher authority.

May I ask you to supply me with the attitude of the Committee on Medical Research toward human experimentation in general, and toward the particular problem of human experiment in the chemical prophylaxis of gonorrhea.

Reply of A. N. Richards, Chairman, to Dr. J. E. Moore October 9, 1942

In your letter of October 6th you ask that I advise you of the attitude of the Committee on Medical Research toward human experimentation in general, and toward the particular problem of human experiment on the chemical prophylaxis of gonorrhea.

The Committee on Medical Research will hold its next meeting on October 29th. I shall present your question to them at that time. In the meantime I have confidence that the Committee will support me in the statement that human experimentation is not only desirable, but necessary in the study of many of the problems of war medicine which confront us. When any risks are involved, volunteers only should be utilized as subjects, and these only after the risks have been fully explained and after signed statements have been obtained which shall prove that the volunteer offered his services with full knowledge and that claims for damages will be waived. An accurate record should be kept of the terms in which the risks involved were described.

In answer to the second part of your question which concerns this specific case, the Committee on Medical Research must rely on the judgment of the Responsible Investigator, supplemented by the judgment of the committee in whose field the investigation is proceeding.

R.G. 227, OSRD, CMR, General Records, Box 43, "Human Experim. — VD" & Fold.

COPY

evision of Dr. Richards' letter of October 9, 1942)
eply of A. N. Richards, Chairman, To Dr. J. E. Moore October 31, 1942

In your letter to me of October 6 you raised the question of the attitude f the Committee on Medical Research toward human experimentation in general and toward he particular problem of human experiment in the chemical prophylaxis of gonorrhea. I gave you a tentative reply under date of October 9 and brought the matter before the MR at its meeting on October 29.

The statement in the second paragraph of my letter of the ninth referring to the general attitude was upheld.

> "Human experimentation is not only desirable, but necessary in the study of many of the problems of war medicine which confronts us. When any risks are involved, volunteers only should be utilized as subjects, and these only after the risks have been fully explained and after signed statements have been obtained which shall prove that the volunteer offered his services with full knowledge and that claims for damages will be waived. An accurate record should be kept of the terms in which the risks involved were described."

I was instructed to recall the third paragraph of that letter and to offer in its place something to the following effect:

> Whenever human experiments are planned as part of work called for in an OSRD contract recommended by CMR, the Committee on Medical Research should know in detail what they are. Further, it must be understood that legal responsibility for possible damages rests with the individual in charge of the experiments and the Institution for which he is agent. Arrangements can be made whereby both he and the Institution can be protected by insurance.

Hoping that the above statements provide adequate answer to your questions, I am

Reply of J. E. Moore, M. D., to Dr. A. N. Richards November 2, 1942

Thank you for your letter of October 31 outlining the attitude of the mittee on Medical Research toward human experimentation. I have forwarded a copy your letter to Doctors C. M. Carpenter of Rochester, New York, and to Alfred Cohn New York City, both of whom are interested in the possibility of human experimation in gonorrhea, though neither have as yet an OSRD contract for this purpose.

&

Serial No. 334
X:CA
CONFIDENTIAL

All/P3-1 (430306) (SC)

March 6, 1943

From: The Chief of the Bureau of Medicine and Surgery.
To : The Officer-in-Charge, Naval Laboratory Research Unit No. 1, University of California, Berkeley, California.
Via : The District Medical Officer, Twelfth Naval District and Naval Operating Base, San Francisco, California.

Subject: Proposed Clinical Evaluation of Influenza Antiserum, and Messages concerning Influenza Virus Specimens.

References: (a) Your letter 4 January 1943.
(b) Your letter of 22 February 1943.

Enclosure: (A) Copy of a preferred form of "release".

1. Following receipt of reference (a), the question of the liability possibly incurred by the Government and/or its agents in carrying out the experimental work proposed in NRS Research Project No. X-102 was referred to the Judge Advocate General's office for expression of opinion.

2. In an informal memorandum, I am advised that the existing release clause is deficient in that it does not state what it releases; that, regardless of form of release executed, all personnel engaged in the tests are subject to action in case negligence can be established; and that such experimentation usually leads to the enactment of special legislation for the relief of any person involved.

3. Further: the evidence available suggests that neither the glycols nor ultraviolet radiation will serve to limit the communication of influenza from individual to individual; and that their ability to sterilize spaces is open to question.

4. In view of the foregoing, the Bureau cannot authorize the experimental exposure of human subjects to influenza virus.

5. It is noted from reference (b) that you inquire whether it would be feasible to send messages to certain investigators abroad from whom you could probably receive suitable specimens for subject experimentation. In view of the action of the Bureau on the subject-request in reference (a) no action will be taken on reference (b).

March 6, 1943

PREFERRED FORM OF RELEASE

"I, _____, of the State Penal Institution, San Quentin, California, being desirous of participating in the experiment to be undertaken by the United States Naval Reserve Laboratory Research Unit No. 1 for the evaluation of influenza antiserum, do hereby certify as follows:

"That I have had explained to me the general purpose and scope of the contemplated experiment the Naval Laboratory Research Unit No. 1 intends to make and for which I am volunteering. I appreciate the fact that there are certain phases of this experiment which for good and sufficient reason cannot be disclosed to me in detail.

"I have had explained to me that there is a certain hazard involved in the procedure and that it is possible that I might become sick and, in a remote case, death might result.

"Having had all of these facts explained to me and being fully cognizant of the fact and circumstances involved and acting freely and voluntarily without any coersion on the part of any person whomsoever, I do hereby consent to the administration of any serum or virus by inhalation or injection into me that the Naval Research Laboratory may desire and the performance upon my body of such experiments as they in their opinion may decide to be of advantage in promoting the research work they are doing.

"I hereby remise, release and forever discharge, the State of California, the individual agencies thereof, the United States of America, its various subdivisions and the individual agencies, officers or other persons conducting the above experiments or in any manner connected therewith, from any and all manner of suits, actions or causes of action, claims or demands whatsoever which I or my heirs, executors, administrators or assigns may at any time have by reason of said experiments or of any results thereof of any kind whatsoever.

"In Witness Whereof I have hereunto subscribed my name this _____ day of 1943.

In the Presence of

_____

_____

_____
Signature."

March 14, 1947

Mr. N. Hilberry — Associate Laboratory Director

Dr. A. M. Brues — Director, Biology Division

Clinical Testing.

I have received, as a member of the Interim Medical Advisory Committee, a letter from Stafford L. Warren who is chairman of this committee, regarding clinical testing. He states:

"At present clinical testing programs have been authorized as a part of the University of California at Berkeley and the University of Rochester contracts only. In the interim period.....it is requested that no other clinical testing be performed by other contractors than has been already authorized.

"This memo refers only to work done under the auspices of, at the expense of, or with equipment furnished by and under the responsibility of the Atomic Energy Commission (and not).....by a doctor upon his own and his university's responsibility and at costs not reimbursable by or not having any connection with the Atomic Energy Commission work".

I am not certain what relation this has to the use of arsenic^{76}, which Dr. Jacobson and Dr. Neal have been preparing through Argonne and are using at Billings Hospital in tracer amounts. I have been assuming that this is part of the approved program of this Laboratory and that the responsibility for the patients was clearly in the hands of the University of Chicago, which Dr. Jacobson assures me is satisfied with the program at Billings.

In the first place, the University of Chicago has been engaged in work using human subjects and related to the work of the Manhattan Project. As reference in this regard, I can cite report No. CH-3607, which was declassified on the last day of 1946, entitled "Distribution and Excretion of Plutonium in two Human Subjects". In the second place, this work is part of the program of the Laboratory as submitted at the meeting of the Medical Advisory Board January 24, 1947, under three of the ten items on this program, namely, (1) Effects of Irradiation on Structure and Functions of the Blood, (2) Response to Different Types of Radiations of Various organs and Tissues including Tumors, and (3) Absorption, Disposition and Elimination of Radioactive Elements from the Body.

The purpose of this work falls under these categories of our program, and it seems to me fortunate that we can parallel our animal observations in humans through the experience and clinical contact of Dr. Jacobson. This work will obviously give us information bearing on the extrapolation of animal work to the human which is most justifiable in the case of this short-lived isotope, which we have good reason to believe may be of actual value to these patients.

I wonder if representations could not be made indicating that this work is an important and consistent part of our program at Argonne and also that the Argonne has included clinical research in its program for some time past.

AMB:bm

Austin M. Brues, M.D.

cc: Reading File

1 - Warren's ltr dated 1/30/47 - indicating UChi approved studies (about him consent of patients - as justification for Arg's program

Dr. Walter J. Williams

Carroll L. Wilson

Medical Research Program

BBosley III

3 - 1947

Attached are copies of a letter dated April 7, 1947 from Dr. Warren to me, and a letter dated April 30, 1947 from me to Dr. Warren, relating to the medical research program. The subjects covered in the letters were discussed with Mr. Tarbell Bulck on his recent trip to Washington. You will note in the third paragraph of my letter to Dr. Warren that the Commission has approved in principle that research personnel working on medical research projects of the Commission should be given an opportunity to devote part of their time to pursuing research on their own initiative, under certain specified conditions. While my letter to Dr. Warren specifies that such research may be approved up to twenty percent of the time of the research personnel engaged on such medical projects, discussions with the Madison Square Area and the University of Rochester have indicated that in some cases, at least, it may be more practicable to compute twenty percent on a budgetary rather than a time basis.

I have already given the Area Manager, Madison Square Area, an authorization to take the action contemplated by paragraph three of my letter to Dr. Warren, and to use either a budgetary or a time basis for computing the twenty percent, in the case of those medical research contracts supervised by his office. It is requested that you take the necessary steps to authorize other Area Managers, who supervise other medical research projects carried on by universities for the Commission, to take comparable action.

Attachments
as stated

(signed) Carroll L Wilson

Carroll L. Wilson

May 6, 1947

Edwin E. Huddleson, Jr.

MEDICAL RESEARCH PROGRAM

Recommend signature attached memorandum to Dr. Walter J. Williams.

Enclosure:
As stated.

CONFIDENTIAL

OFFICE OF THE SECRETARY

Op13C-jc
Serial 67913
April 7, 1943

From: The Secretary of the Navy.
To: All Ships and Stations.

Subject: UNAUTHORIZED MEDICAL EXPERIMENTATION ON NAVAL PERSONNEL

1. It has been noted with concern instances in which service personnel have been subjected to experimental procedures involving potent medication and often hazard to health or efficiency, the investigations in question being conducted by civilian physiologists, civilian physicians, or individual medical officers who may or may not be aware of all considerations pertaining to such investigation.

2. Experimental studies of medical nature upon service personnel are hereby forbidden except when the experimental design in each case has been duly submitted to the Bureau of Medicine and Surgery, for consideration and recommendation, and to the Secretary of the Navy via the Chief of Naval Personnel, the Commandant, Marine Corps, and the Commandant, U. S. Coast Guard for final approval.

FRANK KNOX

As the headquarters should be in the American Medical Association office in Chicago he should be stationed there.

In a recent conference with James Paullin he informed me that the House of Delegates had approved the employment of assistants for carrying on the work of the Committee.

Dr. Lull stated that Dr. Bortz was expected at this meeting of the Executive Committee, but that the railroad strike prevented his coming.

The Executive Committee, on motion duly seconded and carried, voted to refer Dr. Bortz's letter to the full Board and to ask Dr. Bortz to attend one of the meetings of the Board during the San Francisco Session.

INVITATION TO ASSOCIATION TO APPOINT REPRESENTATIVES. Request from War Department for Representative to Go to Europe to Sit on Investigating Commission: Dr. Lull reported that the Secretary of War had received a cable asking him to send representatives to meet with representatives from the allied nations to take certain actions on the human experiments that were carried on there. These experiments have been condemned as morally unsound by the nations themselves and they want them condemned scientifically. The Surgeon General was consulted by the Secretary of War, who stated that they would like to have a representative of the American Medical Association appointed. They telephoned to Dr. Lull for the name of a representative and he telephoned to Dr. Sensenich. They agreed on Dr. Ivy, who is willing to act as the representative of the Association at the conference.

The Executive Committee voted, on motion duly seconded and carried, to approve the appointment of Dr. Ivy to repre-

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sent the American Medical Association to work with representatives from the allied nations at the conference having to do with human experiments.

Board of Trustees: Smith

REPORT OF DR. A. C. IVY ON WAR CRIMES IN WHICH DOCTORS WERE INVOLVED (p. 198): Dr. A. C. Ivy, who was selected by the Board in accordance with a request from the Office of the Surgeon General of the Army to meet with representatives of France and England to make a survey of the war crimes of a medical nature in which German physicians were involved, made a brief report. He stated that the meeting had a two-fold purpose: (1) To make a study of the war crimes and (2) to gather records of all crimes in which doctors were involved so that the medical and scientific world would be objectively informed as to what some of the Nazi physicians and scientists did. The survey was proposed with the idea of (1) making a study showing why these doctors disregarded medical ethics and (2) presenting these facts in book form in which

8.

shall be incorporated a code of ethical rules for experimentation on human beings with the idea that sometime in the future when the international code is being developed the lawyers may desire to say something regarding this matter of human experimentation.

It was fully moved, seconded and carried that Dr. Ivy be asked to turn over to the Secretary and General Manager of the Association an abstract or digest of the scientific evidence regarding brutal human experimentation in Germany during the war for transmission to the Judicial Council with the request that it make a report as to the manner in which these experiments are infringements of medical ethics and that it make a report for submission to the House of Delegates.

REPORT OF DR. A. C. IVY ON WAR CRIMES IN WHICH DOCTORS WERE INVOLVED (p. 8): The Secretary of the Board reported that Dr. A. C. Ivy had met with the Executive Committee in August and had made a report on the survey which he and representatives of France and England made of the war crimes of a medical nature in which German physicians were involved;

51.

that the Executive Committee requested Dr. Ivy to turn over to the Secretary and General Manager of the Association an abstract or digest of the scientific evidence which had been developed in the survey made of war crimes on the part of the Germans during the war, and voted that this report be turned over to the Judicial Council with the request that it make a report as to the manner in which these experiments are infringements of medical ethics and that it make a report for submission to the House of Delegates.

Dr. Lull stated that he had received Dr. Ivy's report and had forwarded it to the Chairman of the Judicial Council.

The Board, on motion duly seconded and carried, voted to approve the action of the Executive Committee in requesting a report from Dr. Ivy and in instructing that it be turned over to the Judicial Council for report.

Reference Committee Transcript for 1946

In regard to the question of Dr. Ivan's report, that was sent to the Judicial Council as a very private, confidential report and it was not on the agenda of our meeting on Saturday, but is on the agenda of our meeting this afternoon and the recommendations will be reported tomorrow and it might be wise to report that recommendation before the Executive Session that we are having.

THE SPEAKER: The report of the Judicial Council then

will be deferred until tomorrow.

Report of the 23-24 January 1947 Meeting of the
Interim Medical Committee of the
United States Atomic Energy Commission

1. Review and Scope of the Medical Research Program.

A. Since the inception of the Atomic Bomb Project, an expanding research program aimed at the diagnosis and control of hazards peculiar to the development of atomic energy has been in effect. These hazards include those injurious effects produced through accidental external body exposure to radiations emitted by various radioactive materials during the experimental or processing operations, as well as the chemical toxicity or localized radiation from such materials deposited within the body.

Considerable preliminary or pilot experimental and clinical information has been obtained by this research program during the last three years. Of necessity, many fields were completely neglected. The injurious effects following single exposures to large amounts of radiation have been determined experimentally; some of the changes following prolonged chronic radiation exposure have been surveyed; the biological effects which follow the introduction of various toxic and radioactive materials into the body have been partially demonstrated. Such pilot studies have been useful in the estimation of maximum allowable exposure levels of radiation or toxic materials to which personnel can be safely exposed for a period of time, and the control of such hazards by the prevention of such exposures. Such standards were designed for war time expediency and are not necessarily applicable to peace time.

While the above information has been extremely useful in this work, it immediately becomes obvious that many critical problems of far reaching scope remain to be solved. Information concerning the method of production of these injurious effects in body tissues is almost completely lacking. No methods are available which might stop or delay the development of radiation injuries. No therapeutic measures are at hand to use following accidental injury due to radiation or radioactive materials. Such problems relate to the fundamental nature of living matter and demand the careful and continued attention of competently trained scientists.

B. The following list indicates briefly the survey of the general studies on radiation effects.

The known radiations encountered in nuclear fission, as well as those encountered from naturally radioactive substances diride themselves into the following types: alpha rays, beta rays, gamma rays and neutrons. The literature on the biological effects of x-rays and gamma rays is voluminous and a good deal of background information was obtained from this source. On the other hand, very little had been written about the biological effects of alpha rays, beta rays and neutrons. It became necessary, therefore, to initiate studies to cope with the unique and pressing problems as rapidly as possible.

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The report of the Medical Advisory Committee to the Director of the Medical Division of Manhattan Engineer District of September 9, 1946 contained the following summary of the problems and the methods of approach being used up to the present.

1. The Physical Measurement of Radiation of Various Types. Here it was and still is necessary to develop better methods of accurately measuring and standardizing the dosage of radiation in two vitally important areas (1) the measurement of the extent of any radiation which might be found in an industrial area and (2) in the biological experimentation.

2. The Biologic Effects of Radiation. Because of the known deleterious effect of radiation on the animal organism, it becomes necessary to determine the effect of controlled dosages of the various types of radiation on various animal and plant species, including marine life. Such observations can be used in the control of possible human exposure and have practical use in medico-legal problems arising from contamination by effluents.

Some of the types of biological effects it is possible to study are given below. Only pilot studies have been done on most of these effects.

a. The survival time or percentage reduction in normal life span of different animal and plant species following a given dose.

b. The genetic effects of radiation as manifested in the development of abnormal individuals from changes in the heredity mechanism.

c. Histopathological changes as demonstrated by abnormal changes in the makeup of the various body tissues.

d. Physiological changes produced by the alteration of the normal functioning of living tissues following irradiation.

e. Biochemical and enzymatic disturbances which are the potential sources of these physiological abnormalties.

3. Methods for the Detection of Minimal Radiation Damage are being developed directly from experiments of the above types and are applied to the study of the human individual. These include studies on:

a. Biochemical and enzymatic changes which may be detected and which, if measurable, can be corrected before irreversible damage has taken place. Examples of such changes would be effects on the metabolism of coproporphyrins, excretion of abnormal substances in the urine, and the like.

b. It has been known that radiation depresses the function of the hematopoietic system (bone marrow, lymph nodes, etc.) and detailed study is indicated to detect early changes under controlled dose radiation with all blood elements under continuous observation.

c. The production of anatomical changes such as epilation, skin erythema, and alterations in the integrity of the skin and the like, must likewise be studied under controlled dosage.

4. Methods for the Prevention of Radiation Injuries. These include:

a. Methods of physical detection of external radiation by the development of sensitive direct reading instruments capable of the detection of amounts of radiation well below those necessary for demonstrable injury to the animal or human subjects.

b. Methods for the determination of harmful amounts of radioactive dusts and gases in air, in water and in body tissues. Many radioactive materials are deposited in the body, like radium, and in such locations produce injury to tissue, particularly the bone marrow. Methods based on the determination of dangerous amounts of these substances by examination of the excreta and direct measurements of the body itself are first developed in animals and then applied to human beings.

5. Protective Measures. Studies on (1) the efficiency of shielding against radioactive materials (2) the efficiency of exhaust and ventilating systems against dangerous amounts of dusts (3) the development of protective clothing and devices and (4) the development of remote control processing methods have been extremely important in the Manhattan District protection program to date and will continue to be fundamental to the development of a safe atomic power program.

6. The possible treatment of radiation injury deserves extensive study with high priority. Experimental replacement of the damaged hematopoietic elements destroyed by severe radiation exposure offers one possibility. Detection and neutralization of hypothetical but unknown toxic substances produced by radiation is another possibility. This difficult and fundamental problem deserves consistent and detailed study.

All the above studies are of necessity done with alpha, beta and gamma rays and neutrons of varying intensity, singly and in various combinations. Also, the effects of acute and chronic exposure must be determined separately because of their dissimilarity.

C. The following list indicates briefly the study of the hazards due to special materials. For brevity, it is preferable to discuss the potential toxicity of special materials by first indicating the types of studies to be carried out, and then by listing those materials on which studies have been made or on which studies are necessary.

1. First, an actual determination of the toxicity of a substance must be made, measuring how poisonous it is, both in acute and in chronic exposures. The amounts administered are decreased until asymptomatic levels are found. In this way, toxic levels may be avoided in laboratory and plant environments. Some pilot work in this direction has been completed for a few compounds of uranium, plutonium and certain special oils.

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a. The mode of entrance into the body (ingestion, inhalation or skin absorption) must be studied as different manifestations and degrees of toxicity may be produced by each route employed. Storage in and excretion from the body must be studied in chronic experiments at various levels of exposure.

b. A careful analysis must be made as to the character of the biological changes; specifically, production of physiological, histopathological and biochemical and genetic evidences of damage. Some progress has been made here.

c. The nature of these injuries and the mechanism by which they occur must likewise be studied. This affords information as to the necessary protective measures, and indicated therapy after exposure. Very little has been attempted here except in one or two instances.

2. Preventative measures require study.

a. The comparative effectiveness of physical methods for the removal of hazardous dusts; namely, the reduction in skin contact and prevention of ingestion, must be measured. Methods for accurate estimation of such hazards must be developed and used. The efficiency of certain protective chemicals, ointments, etc., must be studied. Only pilot studies have been done here.

b. Protective devices such as portable respirators and clothing must be tested for those hazardous substances against which they will be used. No practical mask, military or otherwise, which will protect against some of the worst hazards has been found yet.

c. Finally, appropriate investigation must be made of those therapeutic measures to be used in the treatment of both acute and chronic toxicity states.

3. Completion of the various phases of the program outlined above would provide complete information as to those medical aspects which must be taken into account in the protection of the worker, as well as treatment of injury should it occur. The following is a nearly complete list of the substances on which studies of this type are necessary:

a. Uranium and its compounds.

(1) Uranium metal and its chemical compounds: oxides, nitrate, chlorides, bromide, tetra and hexafluoride, sodium and ammonium diuranates. Some pilot studies have been completed.

(2) Uranium chain of heavy metals:

Uranium X^1
Uranium X^2
Radium
Polonium

Relatively little has been accomplished here.

(3) Fission products of cleavage of U-235 and plutonium. Very meagre pilot studies have been done here.

(4) Artificial isotopes of uranium - 232, 234, etc. Almost nothing has been done here.

b. Thorium and its chain, almost unknown.

c. Plutonium - some pilot work.

d. Special accessory materials - pilot work only.

(1) Fluorocarbons

(2) Fluorine

(3) Beryllium

(4) Others

D. Production Hazards. The results of the laboratory studies made on the materials discussed above are applied to the prevention and control of industrial hazards which arise in the large manufacturing areas where these materials are used in large amounts. These are illustrated by the following:

1. In the Electromagnetic and Diffusion Methods for the isolation of uranium 235, the major hazards are from the uranium compounds, the concentration of uranium X1 and X2, and the special accessory materials and by-products formed in the process of manufacture.

2. In the graphite pile where plutonium (239) is produced on a large scale, the hazards are from the alpha, beta dn gamma rays, neutrons, the plutonium metal and its compounds, the various radioactive fission products resulting from the pile operation.

3. The chemical isolation of polonium following its formation in the pile incorporates hazards from alpha radiation following absorption into the body.

4. Chemical purification process in making uranium metal results in hazards from alpha, beta and gamma radiation and the chemical toxicity of the uranium or other products used.

5. Study of the medical aspects of plant programs aside from the determination of the effect of radiation and chemical toxicity, include additional information obtained from plant investigations as from:

a. Clinical survey of all exposed personnel.

b. Monitoring of hazards by special instruments and methods.

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c. Surveys of new types of graphite piles and production equipment.

E. Hazards of Atomic Catastrophe in Production Areas.

1. Immediate effects:

a. Radiation. The radiation occurring at the time of the explosion coupled with blast and heat causes biological effects which may differ from those occurring following other acute known effects from gamma and neutron radiation, and demand study. Some pilot work and observation of the Japanese indicate that this may be so.

b. Blast. The total blast energy of atomic explosion is very great and may have totally different types of shock waves, recoil waves from ordinary explosives and unique biological effects may be produced. Some pilot work has been done.

c. Actinic Radiation. The intense burns from actinic type of radiation have not been studied. This also includes the combination effect of all three items in this group: blast, radiation and heat.

2. Delayed Effects.

a. Protective devices. Study of methods of protection against the radioactivity deposited at the time of blast.

b. Decontamination. Methods of decontamination of soil and the like must be worked out for cleaning up active areas. Some experience is available on this from New Mexico and the ships from Bikini which is applicable.

c. Investigative equipment. Special equipment must be developed and tested for use in investigating bombed areas.

d. Study of casualty effects. Field study of fission clouds, possible injury to water supply, soil and the like, human damage by population surveys.

e. Study of treatment of all immediate effects such as radiation, heat and blast.

F. Preparation of pertinent information in proper form for use by catastrophe units in production areas.

II. Current Medical Research Program.

A. To permit continuity, it is recommended the current program be continued during 1947-1948. The current program is reviewed by topics under the following list of the participating organizations:

Argonne National Laboratory
University of Rochester
University of California at Berkeley

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Columbia University
University of Washington
Monsanto Chemical Co. (Clinton Lab) USPHS
Monsanto Chemical Co. (Dayton)
Los Alamos
Western Reserve University
University of California at Los Angeles
University of Tennessee
University of Virginia

Brookhaven and other future laboratories are not included.

B. Future expansion of the medical and biological research program on a long term contract basis (5 years or more) is necessary in order to secure information of a more fundamental character which is necessary in order to cope with the special hazards of atomic energy development. Also it is imperative to open new fields of application for the products of atomic energy in biology and medicine. The Committee feels that such expansion can best be planned and put into effect after the establishment of a Medical-Biological Division. (See Appendix A). After the Regional Laboratories are well organized, the obvious usefulness of isotopes in a wide application to biological research will offer so many tremendous opportunities that developments in this field are assured.

C. Specific Projects: (in brief, topical outline)

1. Argonne National Laboratory - Dr. Austin M. Brues, Director.

a. The physiological picture of animals exposed to acute and chronic irradiation.

b. The effects of irradiation on the structure and functions of the blood and on the hematological defenses against infection.

c. The acute toxic effects of external radiation and absorbed radioactive substances: their mechanism of injury; prevention of possible damage and treatment of already injured individuals.

d. The abnormal responses of blood cells, cultured tissue cells and single celled organisms to various types of radiation.

e. The chronic effects of radiation and radioactive materials in animals.

f. The mode of action of radiation in the production of cancer.

g. The response to different types of radiation of the various organs and tissues, including tumors.

h. Studies on the chemical effects of radiation which are fundamental to its biological response.

i. The absorption, deposition and elimination of radioactive elements from the body.

j. The design and standardization of instruments to carry out the foregoing.

2. University of Rochester - Dr. Andrew H. Dowdy, Director.

a. Radiation and Radiology Section:

(1) Instrument design, measurement standardization, industrial monitoring.

(2) Biological effect of tracer amounts of polonium, radium and uranium in human and animal subjects. Application of tracer experiments to serve other parts of the project.

(3) Physiological effects of exposure to acute and chronic radiation including the radio-isotopes; search for therapeutic methods of value.

(4) Development of possible chemical techniques or methods of detection of radiation damage, and the mechanism by which such effects are produced.

(5) By means of spectroscopic methods, to study the distribution of uranium and other heavy metals of importance in animal tissue; a search for possible clues as to the method of bony deposition of radioactive materials.

(6) Study of the time intensity factor in radiation, and development of methods of producing instantaneous exposure to radiation (A bomb effect).

(7) Study of the metabolism of plutonium, polonium, radium, etc., in human subjects.

b. Pharmacology:

(1) Study of the inhalation toxicity of various uranium, beryllium and thorium compounds. Studies in the mechanism of production of inhalation toxicity.

(2) By chemical techniques, studies of the mechanism of uranium fixation in bones, uranium complex formation, methods of excretion of uranium.

(3) Acute toxicity effects of uranium, beryllium and thorium compounds by ingestion.

(4) Pathological effects of uranium, beryllium and thorium poisoning, and mechanism by which produced.

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(5) Physiological effects of uranium, beryllium and thorium poisoning.

(6) Special toxicity studies.

(7) Certification of respiratory protective devices.

c. Experimental Surgery.

(1) Clinical, hematological and pathological effects of acute lethal radiation.

(2) Methods of bone marrow transplantation.

(3) Studies in bone marrow reserve and radiation effect.

(4) Tissue culture studies related to bone marrow production.

(5) Effect of folic acid and rutin on marrow regeneration.

(6) Studies of metabolism of iodine by thyroid.

d. Experimental Hematology.

(1) Comparative study of blood histamine after radiation and hematological effects in cells.

(2) Studies of life cycle of blood platelets.

(3) Studies on life cycle of leukocytes.

(4) Studies on marrow reserves after radiation.

(5) Evaluation of coagulation defects following irradiation.

(6) Techniques for early detection of hematological changes resulting from ionizing radiation.

e. Genetics.

(1) Continuation of studies of effect of chronic radiation on mice.

(2) Continuation of studies on effect of acute and chronic radiation (x-ray) on D rosophilia.

(3) Histogenetics.

f. Training personnel in all above sections.

3. University of California at Berkeley.

a. Dr. Joseph Hamilton's program.

(1) Metabolism of fission products, radium, actinium, protoactinium, uranium, neptunium, plutonium, americium and curium in animals and man.

(2) Metabolism of possibly hazardous artificially induced radioactive elements from plant construction materials such as chromium, nickel, etc.

(3) Metabolism of beryllium.

(4) Development of methods of treatment of poisoning from fissionable elements, notably plutonium and uranium 233 and from the long lived fission products.

(5) Behaviour of fission products and fissionable elements in soils and plants.

(6) Study of alpha particle irradiation and the thyroid gland in animals and man by Asticine (Element 85).

(7) Development of methods for decontamination of radioactive ships from Operation Crossroads.

(8) The execution of certain radio chemical analyses for Operation Crossroads and training of Army and Navy personnel.

(9) A study of the metabolism of elements chemically similar to the fissionable elements and the fission products.

b. Dr. John H. Lawrence's program.

(1) Biological effects of fission products.

(2) A search for uranium compounds that will localize in organs other than the liver and spleen.

(3) Biological effects of the disintegration products of boron and lithium following neutron irradiation.

(4) Genetics of the carcinogenic effect of beta rays.

(5) Physiological chemistry of the biological action of radiations.

(6) Changes in water balance following radiation injury.

(7) Radiation effects on tissue cultures.

(8) Effects of selective irradiations of individual organs and tissues.

c. Dr. Robert S. Stone's program.

(1) Studies in whole body radiation of human subjects by external and internal radiation.

(2) Studies on the metabolism of radioactive iodine in animals and man.

(3) Joint studies with Dr. Joseph G. Hamilton to evaluate the therapeutic applications of the fission products and the fissionable elements.

(4) Exploration and therapeutic applications of other radioactive elements and compounds.

4. Columbia University - Dr. G. Failla, Director.

a. Measurement offast neutrons for biological purposes.

b. Measurement of time dose relationship resulting from radioactive isotopes distributed in the tissues.

c. Measurement of specific gamma ray emission.

d. Study of the quantitative relationships in chemical effects produced by gamma rays and fast neutrons.

e. Further study of eye and gonad injury produced by fast neutrons.

f. Study of the biological action of ionizing radiations.

g. An attempt to reduce radiation injury.

h. Study of the distribution of radioactive isotopes in tissues and cells.

i. Protection data for the safe handling of radioactive isotopes in small amounts.

j. Training of personnel.

k. Measurement of very high energy radiations for biological dosage.

5. University of Washington School of Fisheries - Dr. Lauren R. Donaldson, Director.

a. The work of this project is to explore the general problem of the effect of radiation on aquatic organisms, and in particular, to study the problems arising from the discharge effluent from the Hanford plants into

the Columbia River and the possible contamination of sea water (including Bikini). The work under this contract involves studies of the following nature:

(1) Acute and chronic effects of external radiation on fishes.

(2) Breeding studies on salmon and trout following irradiation.

(3) Studies of the effects of the Hanford effluent on salmon and trout.

(4) Effects of internally deposited radioactive materials on aquatic organisms.

(5) Field studies on the effect of possible Hanford pollution on aquatic life in the Columbia River.

(6) Studies on the transfer of radioactive materials in "food chains", starting with the simpler biological forms (i.e. plankton) and following the distribution and fate of such materials as these contaminated animalcules are successively eaten and metabolized by higher forms (fishes, etc.).

(7) Feeding experiments using radioactive materials in the foods.

6. Hanford Engineer Works (Research Project) - Dr. Simeon T. Cantril, Director.

a. Health physics research and development in radiation monitoring, instrumentation.

b. Training of technicians and other personnel in problems of radiation protection.

c. Applied biologic research relative to phases of radiation hazard peculiar to Hanford Engineer Works operations and waste disposal:

(1) Soil, water and air contamination by radioactive materials

(2) Studies under controlled conditions of the effects of radioactive materials on domestic animals.

(3) Studies under controlled conditions of the effects of radioactive materials on vegetation.

(4) Fish Studies: (In collaboration with University of Washington, project listed previously.)

(a) Effects of waste effluent on salmon and trout.

(b) Effects of internally deposited radioactive materials.

(c) Field studies on possible pollution of Columbia River and fish by Hanford waste.

(d) Plankton experiments - absorption studies.

7. Monsanto and U. S. Public Health Service, Clinton Laboratories - Dr. Alexander Hollaender, Director.

a. Studies of the biological effects of slow and fast neutrons, beta and gamma radiation are in progress as a follow-up of previously reported work.

b. Effects of plutonium on bone healing is being studied.

c. The parabiotic twin technique is being used to study the indirect effects of radiation.

d. A concentrated attack is being made on radiation effects on the rate of mitosis, chromosome breaks and exchanges, gene mutations and the general genetical makeup of the cell, including cytoplasmic factors.

e. Tracer experiments of a number of metabolic systems have been initiated using various micro-organisms.

f. Effects of radiation on cell constituents, proteins, nucleic acids and enzymes are being studied by modern physical-chemical tools, (including isotopes.)

g. Radiation effects are being investigated on blood constituents and blood forming organs as well as on the nervous system.

(h) Cooperative research arrangements are being made with the Universities of Tennessee, Vanderbilt University, Washington University, University of Pennsylvania, John Hopkins University and Carnegie Institution.

(i) Close cooperation with the National Institute of Health and the National Cancer Institute has been set up.

j. Instrumentation of radiation monitoring developed by health physics will be continued.

k. Health physics research is to be extended.

l. A training program.

8. Monsanto Chemical Co. (Dayton) - Dr. James Svirbely, Director.

a. Biological effects of chronic and acute exposures to polonium and polonium compounds by various modes of administration to determine the maximum permissible levels for human exposure. Tracer experiments may be indicated for clinical investigation. Mechanism of action, correlation of excretion levels with visceral content and genetic effects will be studied.

b. Maximum permissible levels for alpha radiation in individual viscera, especially the kidney. This is a specific phase of the first problem.

c. Study of maximum permissible levels for polonium to use in safe waste disposal.

d. Correlation of excretion levels and exposure in production personnel.

e. Study of prophylaxis and therapy of the toxic effects of polonium.

f. Biologic effects and methods of measurement for protection against radiation from special neutron sources prepared at Dayton.

g. Development of continuous monitoring equipment and other types.

h. Studies of the prevention of contamination and on decontamination.

9. Western Reserve University - Dr. Hymer L. Friedell, Director.

a. Studies on toxicity of thorium.

(1) Biological effects.

(a) Study of biological effects of soluble thorium compounds, lethal effects, weight changes, histopathologic, hematologic and biochemical changes.

(b) Study of biological effects of insoluble thorium compounds as in a(1) above, but also includes radiation effects.

(2) Distribution studies.

(a) Study of thorium distribution in tissues by chemical assay.

(b) Study of distribution by tracer technique.

(3) Biochemical studies.

(a) Transport of thorium across gastro-intestinal and respiratory epithelium.

(b) Mode of transfer of thorium in blood and tissues.

(c) Manner and characteristics of thorium deposition in tissue.

(d) Review of enzyme systems affected and enzyme inhibition.

b. Study of radiation effects of internally distributed radioactive elements.

(1) "Summation" studies of several radioactive elements of widely varying specific ionization.

(a) Study of beta emitters lodging in specific tissues (bone, kidney, thyroid, etc.).

(b) Study of alpha emitters lodging in specific tissues (bone, kidney, thyroid, etc.).

(c) Comparison and summation of alpha and beta emitters having approximately similar deposition in tissue.

c. Synthesis of compounds into which radioactive elements may be introduced.

(1) Comparison of radiation effects of various beta emitters alternately introduced into the same compound.

(2) Comparison of radiation effects of beta and alpha emitters (wide divergence of specific ionization) alternately and concomitantly introduced into the body.

d. Study of the distribution of the above noted radioactive compounds.

(1) By assay of radioactivity in tissues.

(2) By radioautographs of tissues and similar suitable means.

10. Los Alamos - Dr. Louis Hemplemann, Director.

a. Plant hazard research.

(1) Development of method for the determination of minute amounts of plutonium in the excreta and body tissues of humans and animals.

(2) Determination of the fraction of injected plutonium excreted per day by humans and animals. (In collaboration with the University of Rochester).

(3) Metabolism of plutonium in animals.

(4) Hematological studies in laboratory personnel exposed chronically to small repeated doses of radiation and radioactive material and accidentally exposed to large doses of radiation.

(5) Development of instruments to measure radiation.

(6) Development of safe techniques for plant operation.

(7) Clinical studies on acute radiation disease.

b. Proposed fundamental and applied research program.

(1) The fundamental studies on the acute effects of radiation.

(2) Treatment of acute radiation disease.

(3) Methods of detecting early radiation injury.

(4) Continued studies of the metabolism of plutonium, U-235 and other radioactive materials.

(5) Detection of accumulated plutonium in the lungs.

(6) Biochemical studies of nucleoprotein and the effect of radiation of the fundamental physiology of the cell. (In collaboration with Washington University, St. Louis, Mo.).

(7) Detailed study of absorption of plutonium from contaminated surfaces and wounds.

(8) Any special problems arising from new operating hazards on this project.

11. University of California at Los Angeles - Dr. Stafford L. Warren, Director.

a. The mechanism of blood vessel injury by radiation.

b. Bone marrow injury by radiation, its repair and treatment.

c. Mechanism of "metal" deposition in bone and mechanism of removal from bone.

d. Protein degradation following radiation and chemical injury.

12. Contracts approved by the Interim Medical Committee and awaiting U. S. Atomic Energy Commission approval:

a. University of Virginia - Dr. Alfred Chanutin, Director.

(1) Study of the effects of various types of radiation (alpha, beta, gamma and neutrons) on the circulating blood proteins by electrophorosis and protein fractionization technique. To determine whether means of early detection of radiation damage can be accomplished in this way.

b. University of Tennessee - Dr. Henry Wills, Director.

(1) Study of the mechanism of toxic effects of uranium and other heavy metal compounds on the kidney. This is a continuation of Dr. Wills' work with the Rochester Manhattan Project during the war and contributes to that general study.

D. Estimated total Health-Safety research budgets for fiscal year 1946-1947 and 1947-1948.

1.

Contractor	Fiscal Year 1946-1947	Fiscal Year 1947-1948	Probable Local Budget
Los Alamos	$ 100,000.	$ 200,000.	$ 500,000.
Univ of Rochester	1,200,000.	1,300,000.	1,800,000.
UofC at Berkeley			
Program II 3a	100,000.	125,000.)	
II 3b	115,000.	200,000.):-	400,000.
II 3c	20,000.	35,000.)	
Clinton Lab	180,000.	500,000.	500,000.
Monsanto (Dayton)	40,000.	225,000.	200,000.
Hanford	200,000.	500,000.	500,000.
Western Reserve	100,000.	155,000.	200,000.
U of Washington	28,000.	100,000.	150,000.
Columbia University	100,000.	100,000.	100,000.
Argonne	1,200,000.	1,400,000.	1,500,000.
Brookhaven		400,000.	500,000.
U of Virginia	25,000.	50,000.	50,000.
U of Tennessee	16,000.	16,000.	16,000.
UofC at Los Angeles	100,000.	200,000.	200,000.
Western Regional		400,000.	500,000.
Total Medical-Biological	$3,524,000.	$5,906,000.	$7,116,000.
Health-Physics	500,000.	1,000,000.	1,300,000.
Training	(?) 50,000.	5,000,000.	1,750,000.
Field Survey & Service Research	(?) 3,000,000.	2,000,000.	3,000,000.
Estimated Grand Total	$7,074,000.	$13,906,000.	$13,166,000.

Note: See D2 for estimated totals of Regional Laboratories including budgets for research in the participating universities. Only those currently active are shown.

2. Eventual Health-Safety research budgets, 1949-50. Estimated annual budget for research. Does not include monitoring or clinical services which are charged to operating budgets. Each Regional Laboratory budget represents the totals of the local research and those of the participating universities.

Regional Laboratory	Training	Biological-Medical	Health-Physics	Field Survey and Service Research
Argonne	$500,000.	$4,000,000.	$ 250,000.	$ 100,000.
Brookhaven	500,000.	4,000,000.	250,000.	1,425,000.
Clinton Lab	250,000.	1,000,000.	250,000.	200,000.
Hanford	100,000.	1,000,000.	100,000.	50,000.
Los Alamos	200,000.	750,000.	250,000.	25,000.
Western	200,000.	1,000,000.	200,000.	100,000.
Total	$1,750,000.	$11,750,000.	$1,300,000.	$2,000,000.
Grand Total				$16,800,000.

This total should be equivalent to approximately 20-25% of the total research effort of the U. S. Atomic Energy Commission.

3. Example of estimated Medical Research Budget for a Regional Laboratory. 1949-50.

Brookhaven	Training	Medical-Biological	Health-Physics	Field Survey and Services
Local	$ 100,000.	$1,000,000.	$ 50,000.	$ 50,000.
Rochester	175,000.	900,000.	25,000.	700,000.
Columbia	25,000.	200,000.	25,000.	50,000.
Cornell	25,000.	200,000.		
Harverd	50,000.	200,000.	25,000.	
Yale	25,000.	200,000.		
M.I.T.	50,000.	200,000.	50,000.	50,000.
Princeton	25,000.	50,000.		
Brown		50,000.		
Others	25,000.	1,000,000.	25,000.	500,000.
Total	$ 500,000.	$4,000,000.	$ 200,000.	$1,425,000**

*May be directed into new or above affiliated group as need arises for investigation of certain problems.

**This total is large because this area carries the major industrial and production activities.

III. Health-Physics.

A. Health-Physics is the name applied to a newly developed and highly specialized branch of Radiology. The principal function of Health-Physics has been to make a study of radiation problems and to devise means of preventing radiation damage. The records obtained by this group are of medico-legal importance. The manpower shortage in this field is acute.

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In general there are two principal sections in each health-physics division:

1. Research and development in instrumentation and energy levels.

2. Service under operating conditions in the plant.

B. The duties of the service section of health-physics are:

1. Personnel monitoring the measurement and recording of the daily radiation dosage received by each person.

2. Instrument service.

a. The calibration and maintainance of the varied and numerous instruments employed.

3. Building surveys. A daily measurement and recording of working areas.

4. Off-area surveys. An approved monitoring of the radiation level in the air and water discharged from the plants so that it presents no hazard to neighboring communities. The cost of the service sections of health-physics should be borne by each plant as an operating cost. Only the costs of the research and development sections are indicated in Section II D1 and 2.

C. The problems of the research and development sections of the health-physics divisions have been quite varied and perhaps can be indicated best by the following list which presents a few typical examples:

1. Instrument development.

a. Personnel monitoring instruments such as pocket meters and film badges have been developed but still need improvement.

b. Many problems were encountered in the development and production of fairly suitable portable and fixed meters to measure the alpha, beta, gamma, thermal neutron and fast neutron exposures received by personnel under varying situations.

c. Survey meters of all types, especially electrostatic and electronic instruments were developed and produced. These need considerable improvement, particularly for alpha and neutron measurements.

2. Special measurement of energies to which personnel is exposed.

a. Relative to instruments:

(1) Test meters for energy dependence and saturation effects.

(2) Develop photographic film monitoring techniques.

(3) Develop an instrument to measure fast neutrons in the presence of gamma rays.

(4) Devise methods of measuring plutonium in air in the presence of other alpha emitting substances.

(5) Develop continuous air monitoring instruments to measure alpha, beta and gamma radioactive gas and suspended dust in the air.

(6) Develop automatic hand counters, area radiation warning instruments, automatic water activity counters, etc.

b. Applied physics measurements.

(1) Develop remote control operations for working with radioisotopes.

(2) Make a study of various types of shielding, radiation shipping containers, etc.

(3) Develop methods of determining the amount of plutonium, polonium, uranium, etc., that are fixed in the body.

(4) Develop methods of estimating excessive radiation exposures from the amount of radioactive sodium and potassium in the blood.

(5) Measure the efficiency of masks, respirators, gloves, and clothing in preventing body radiation exposure.

(6) Develop and operate methods of decontamination.

(7) Study new methods of radioactive waste disposal.

(8) Help in the design of new buildings to minimize radiation exposure.

c. Physics research.

(1) Carry out "sky-shine" experiments.

(2) Study effects of high energy radiation on tissue.

(3) Study radiation scattering in shields and in tissue.

(4) Determine value of n/r, etc.

d. Theoretical.

(1) Make numerous tolerance calculations to determine radiation hazards presented by external and internal exposure.

(2) Calculate radiation from extended sources.

(3) Set up radiation protection tables, rules, regulations, etc.

e. Educational program.

(1) Train health physicists for other atomic energy sites, for those universities and laboratories that have radiation problems, as well as for the Army and Navy.

(2) Consult with numerous individuals and committees on radiation problems.

(3) Help outside organizations to check their laboratories and operations for radiation hazards.

(4) Train chemists, physicists, etc, who are not health physicists but who need a proper respect for radiation problems.

(5) Operate health-physics training programs. This is urgently needed. None are available now.

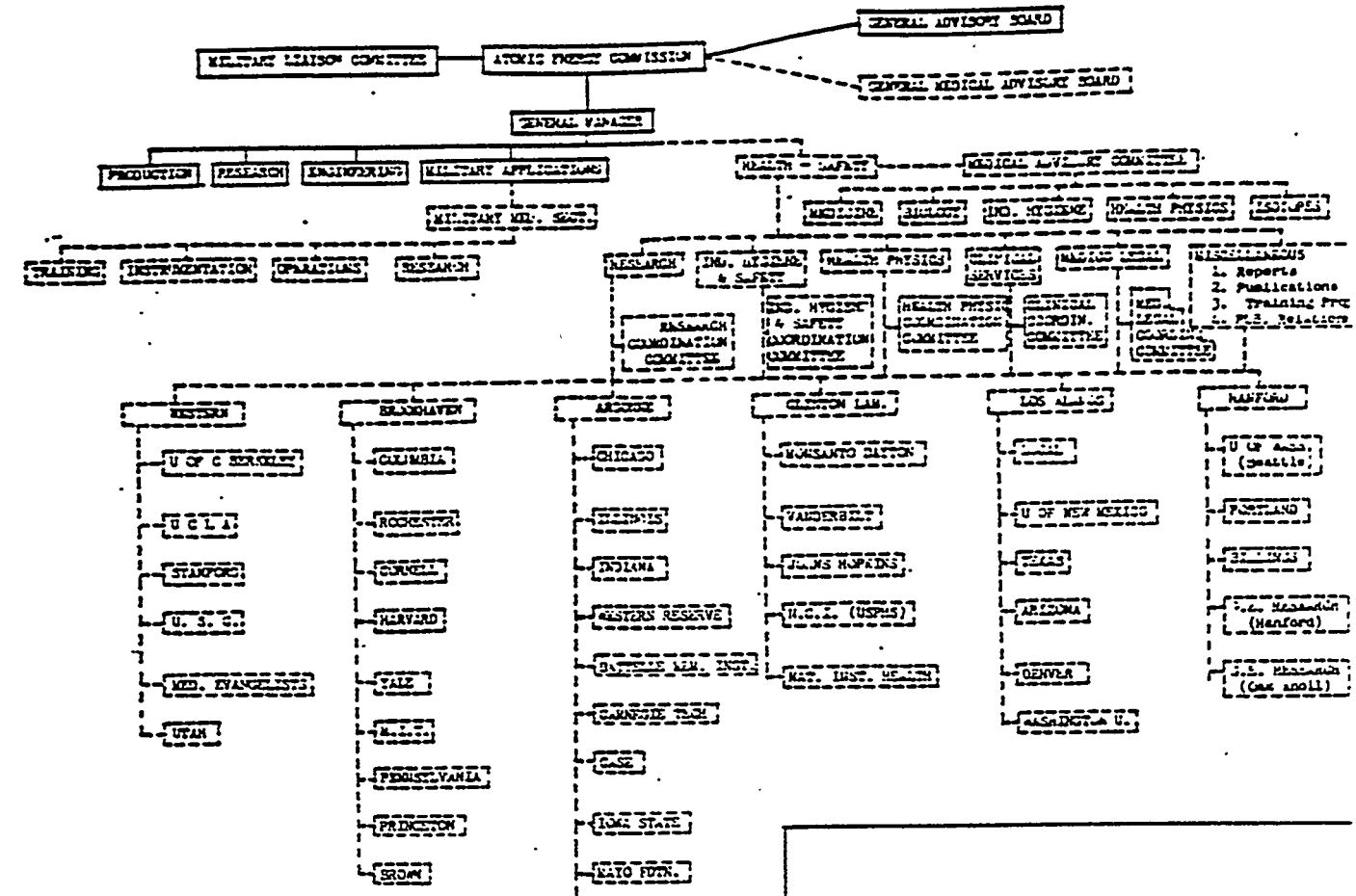
D. The table in Section II D1 and 2 gives an indication of the present and future total manpower and total expenditures of health-physics. Past annual costs have been quite large but are not available.

IV. Training program.

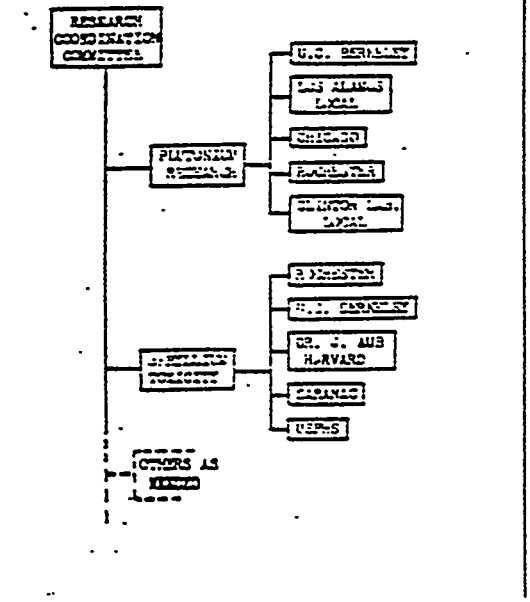
A. One of the most serious difficulties impeding the immediate progress of the general program designed to safeguard civilian and industrial personnel against the deleterious effects of the products of nuclear energy and the promotion of the beneficial utilization of such products is the lack of a sufficient number of well-trained personnel. Such a situation has arisen from the combination of a hiatus in basic science training during the war and the uniqueness of the problems confronting the Atomic Energy Commission.

It is recommended that an extensive training program be sponsored by the Atomic Energy Commission to facilitate the training of suitable personnel in the various branches of atomic energy. As a result of the crowding of the universities, some building program will probably be necessary. Such a program should embody the following objectives:

1. To increase the usefulness of present project personnel, academic seminars should be instituted and in certain instances, attendance of courses in the basic sciences of physiology, histology, biology, physics, bio-physics, chemistry, etc, should be required as a part of their regular scheduled duties.



SUGGESTED EXAMPLE OF TYPICAL COORDINATION COMMITTEE AND SUB-COMMITTEES



1. The suggested personnel for the General Medical Advisory Board appears on page 22 of the report of the 23-24 January 1947 meeting of the Interim Medical Committee of the United States Atomic Energy Commission.

2. The list of names suggested for the position of Director of the Division of Health-Safety appears on page 23 of the 23-24 January 1947 meeting of the Interim Medical Committee of the United States Atomic Energy Commission.

3. The suggested personnel for the Medical Advisory Committee and its sub-committees of Medicine, Biology, Industrial Hygiene, Health Physics and Isotopes are listed on pages 24 thru 27 of the 23-24 January 1947 meeting of the Interim Medical Committee of the United States Atomic Energy Commission.

4. It is suggested that the Military Medical Section under the division of Military Application have members representing all armed services.

5. The Coordination Committees shown under Research, Industrial Hygiene & Safety, Health Physics, Clinical Services and Medico-legal should each be composed of the 6 regional Directors or their authorized representatives plus 3 outside competent men. The personnel of the necessary sub-committee under each of these Coordination Committees should be proposed by the Coordination Committee as conditions warrant, and be representative of major topics under research for proper horizontal evaluation.

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APPENDIX A

AGENDA FOR MEDICAL COMMITTEE FOR ATOMIC RESEARCH

JANUARY 23, 24, 1947

I. Review and approval of past program. (Medical summary 1943-46 to be reviewed and approved if possible).

II. Scope of Research Program 1946-47. (Appendix A)

(University of Chicago) Argonne National Laboratories
University of Rochester
University of California
Hamilton
Stone
Columbia University
University of Washington, Seattle
Monsanto Chemical Corp. (Clinton Laboratories) USPHS
Monsanto Chemical Corporation (Dayton)
Los Alamos
Western Reserve University

Contracts Awaiting Approval:

University of Virginia
University of Tennessee

III. Recommendations for Future Research Policy

A. Scope of fundamental work (that approved in September meeting) (Appendix A)
B. Human Testing with special materials

IV. Organization of Medical Responsibilities

A. Advisory Committees

1. Advisory Committee on Medical Research and application (Tolerances, Standards and Hazard Interpretations in addition to research programs).
2. Advisory Committee on Industrial Medicine and Toxicology.
3. Advisory Committee on Health Physics.

B. Recommendation for the continuation of operation of the Medical Division at the present level with the available reduced force now in that office as well as salary schedule.

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C. Training Program

1. Statement of the urgent need for qualified trained physicians.
2. Source of physicians.
   A.S.T.P.
   Civilian
3. Recommendations for specific training program.

V. Recommendations for Medical Director and Delineation of Responsibilities.

VI. Representation on Advisory Board to Atomic Energy Commission

VII. Release of Information

Recommendation for a mass meeting of all present and former Atomic Energy Commission medical researchers, at which time a program (4 days) would present accurate information on all medical aspects related to atomic energy then available for security clearance. This meeting would be open to scientific personnel in all parts of the country. The following suggestions are pertinent:

A. Approximately 6-8 months preparation would be required.
B. A central location should be selected to insure a maximum attendance.
C. Abstracts of the program should be circulated at least one month prior to the date of the meeting (similar to that procedure used by the Federated Societies of Physiology, Biochemistry, etc.) These abstracts should be approved by a previously selected editorial board before release.
D. Consideration should be given toward the founding of a new scientific society whose major interest would be based on problems of radiobiology as related to medical interest. The Journal of Radiobiology now being launched could well be made the official journal of this society.

Types of study include I General Studies in Radiation including (1) physical measurement of radiation, (2) biological effects of radiation (3) methods of detection of minimal radiation damages and (4) methods for the prevention of radiation injuries. II Hazards due to special Materials (for non-radioactive, radioactive and fission materials) (1) degree of toxicity (2) preventative measures. III Special Production Hazards and IV Hazards of Military Uses.

Argonne National Laboratories (University of Chicago)

1. General physiological picture of acute and chronic radiation.
2. Radiation effect on blood clotting, lymphocyte distribution and spread of infection.
3. Toxic effects of external radiation and absorbed radioactivity.
4. Response of blood cells to various types of radiation.
5. Chronic effects of radiation and radioactive materials in animals.
6. Mode of action of radiation in carcinogenesis.
7. Chemical and physiological basis of radiation effects.
8. Metabolism of radioactive elements.
9. Instrument standardization, design, etc.

University of Rochester

Radiation and Radiology Section

1. Instrument design, measurement standardization, industrial monitoring.
2. Biological effect of tracer amounts of polonium, radium and uranium in human and animal subjects. Application of tracer experiments to serve other parts of the project.
3. Physiological effects of exposure to acute and chronic radiations including radio isotopes; search for therapeutic methods of value.
4. Development of possible chemical technique or methods of detection of radiation damage and the mechanism by which such effects are produced.
5. By means of spectroscopic methods to study distribution of uranium and other heavy metals of importance in animal tissue; search for possible clues as to the method of bony deposition of radioactive materials.
6. Study of the time intensity factor in radiation and development of methods of producing instantaneous exposure to radiation (A bomb effect).
7. Study of the metabolism of plutonium, polonium, radium, etc., in human subjects.

Pharmacology

1. Study of the inhalation toxicity of various uranium, beryllium and thorium compounds. Studies in the mechanism of production of inhalation toxicity.

2. By chemical technique, studies of the mechanism of uranium fixation in bones, uranium complex function, methods of excretion of uranium.
3. Toxicity of uranium, beryllium and thorium compounds by ingestion.
4. Pathological effects of uranium, beryllium and thorium poisoning and mechanism by which produced.
5. Physiological effects of uranium, beryllium and thorium poisoning.

Experimental Surgery

1. Clinical, hematological and pathological effects of acute lethal radiation.
2. Methods of bone marrow transplantation.
3. Studies in bone marrow reserve and radiation effect.
4. Tissue culture studies related to bone marrow production.
5. Effect of folic acid and rutin on marrow regeneration.
6. Studies in metabolism of iodine by thyroid (15%).

Experimental Hematology.

1. Comparative study of blood histamine and hematological effects in cells.
2. Studies on life cycle of blood platelets.
3. Studies on life cycle of WBC leukocytes.
4. Studies on marrow reserves after radiation.
5. Evaluation of coagulation defects following irradiation.
6. Techniques for early detection of hematological changes resulting from ionizing radiation.

Genetics

1. Continuation of studies of effect of chronic radiation on mice.
2. Continuation of studies on effect of acute and chronic radiation (X-ray) on Drosophilia.
3. Histogenetics.

University of California

1. Studies of the metabolism of plutonium, uranium and fission products in rats and man.
2. Fission product tracer studies.
3. Metabolism of radium, actinium, americium and curium in animals and man.
4. Studies (pilot) on possibly hazardous artificially induced radioactive elements, i.e. chromium, nickel, etc.
5. Beryllium tracer studies.
6. Treatment of plutonium poisoning.

7. Behavior of fission products in soils.
8. Biological effects of fission recoils.
9. Search for other U compounds which will localize in organs other than liver and spleen (15%).
10. Biological effect of disintegration products of boron and lithium of the neutron irradiation (15%).
11. Study of element 85 in the thyroid (15%).
12. Training of Crossroads personnel.
13. Studies in whole body radiation of human subjects.
14. Studies on metabolism of radioactive iodine in animals and man.

Columbia University

1. Studies on the measurement of fast neutrons for biological dosage.
2. Development of a method of measuring neutron dose by chemical means.
3. Measurement of radioactive isotopes for biological and medical application.
4. Correlation of tissue doses and biological effects produced by external irradiation and by radioactive isotopes internally administered.
5. Exploratory biological experiments to extend use of radio-active isotopes as tracers on therapeutic agents (15%).
6. Studies of the fundamental biological action of ionizing radiation.
7. Measurement of the radiation of radioactive isotopes to provide data for the protection of personnel and films in transit.

University of Washington (Seattle)

1. Acute and chronic effects of external radiation on fishes.
2. Breeding studies on salmon following radiation.
3. Studies on the effects of Hanford effluent on salmon and trout.
4. Effect of internally deposited radioactive materials on fishes.
5. Field studies on the effect of possible Hanford pollution on fish life of the Columbia River.
6. Plankton experiments - effect of radiation on higher forms (new).
7. Feeding experiment on deposited radioactive materials (new).

Monsanto Chemical Corp. (Clinton Laboratories) USPHS

1. Continuation of studies on the biological effect of slow fast and thermal neutrons on rats and mice.
2. Continuation on studies on the comparative biological effect of penetrating radiation.
3. The effect of internally deposited plutonium on bone healing.
4. Cytological program on the biological effect of radiation on simple cells and tissue.
5. Instrumentation and techniques of radiation monitoring.

Monsanto Chemical Co. (Dayton) New program being organized.

1. Biological effects following chronic exposure of animals to polonium by inhalation and parenteral administration.
2. Correlation between chronic exposure of workers and polonium excretion rate.
3. Mechanism of action of polonium toxicity.
4. Development of special health physics technique for specific use in polonium purification.

Los Alamos

1. Fundamental studies on the effect of acute radiation exposure.
2. Treatment of acute radiation disease.
3. Methods of detecting early radiation changes.
4. Metabolism of plutonium, U^{235} and other radioactive materials.
5. Detection of accumulated plutonium in the lungs.
6. Biochemical studies of nucleoproteins and the effect of radiation on the fundamental physiology of the cell.
7. Detailed study of absorption of plutonium from contaminated wounds.
8. Any special problems arising from medical hazards peculiar to this project.

Western Reserve University

1. Investigation of the toxic effects of thorium and its isotopes.
2. Comparative studies on the biological effect of external radiation and that from internally deposited radioactive materials.
3. Use of radioactive isotopes in fundamental biological research.

These general titles are given inasmuch as a program has not been actively formulated.

Contracts Awaiting Approval:

University of Virginia - Dr. Alfred Chanutin

Study of the effects of various types of radiation (alpha, beta, gamma & neutrons) on the circulating blood proteins by electrophoresis and protein fractionization technique. To determine whether means of early detection of radiation damage can be accomplished in this way.

University of Tennessee - Dr. Henry Wills

Study of the mechanism of toxic effects of uranium and other heavy metal compounds on the kidney. This is a continuation of Dr. Wills' work with the Rochester Manhattan Project during the war and contributes to that general study.

APPENDIX A (Cont'd.)

University of California, Los Angeles - Dr. Stafford L. Warren

1. The mechanism of blood vessel injury by radiation.
2. Bone marrow injury by radiation, its repair and treatment.
3. Mechanism of "metal" deposition in bone and mechanism of removal from bone.
4. Protein degradation following radiation and chemical injury.

I General Studies of Radiation

The radiations encountered in nuclear fission as well as those encountered from naturally radioactive substances divide themselves into the following types: Alpha rays, beta rays, gamma rays and neutrons. Information available from the literature on previous studies indicates a rather extensive knowledge of the biological effects of X-rays and gamma rays and very little information on alpha and beta rays and neutrons.

The programs were and are organized using the following basic outline:

A. The Physical Measurement of Radiation of various types - Here it is necessary to develop methods of accurately measuring and standardizing the dosage of radiation to be used in the biological experimentation and measurement of the extent of any hazardous radiation which might be found in a plant area.

B. The Biologic Effects of Radiation. Because of the known deleterious effect of radiation on the animal organism, it becomes necessary to determine the effect of controlled dosages of the various types of radiation on various animal species, so that such observations can be used in the control of possible human exposure.

The types of biological effect possible to study are:

(1) The Survival Time or percentage that the effect of a given dose will reduce the normal life span of different animal species.

(2) The Genetic Effects of radiation as manifested in the development of abnormal individual types from changes in the hereditary mechanism.

(3) Histopathological Changes as demonstrated by abnormal changes in the make-up of the various body tissues.

(4) Physiological Changes produced by the alteration of the normal functioning of animal tissues following radiation.

(5) Biochemical and Enzymatic disturbances which are the potential source of these physiological abnormalities.

APPENDIX A (Cont'd.)

C. Methods for the Detection of Minimal Radiation Damage are developed directly from observation of the above types and are applied to study of the human individual or worker. These include studies on:

(1) Biochemical and Enzymatic Changes which may be detected and which, if measurable, can be corrected before irreversible damage has taken place. Examples of such change would be effects on the metabolism of coproporphyrins, excretion of abnormal substances in the urine and the like.

(2) It has been known that radiation depresses the function of the hematopoetic system and detailed study is indicated to detect early changes under controlled dose radiation with all blood elements under continuous observation.

(3) The Production of Anatomical Changes such as epilation, skin erythema, and alterations in the integrity of the skin and the like must likewise be studied under controlled dosage.

D. Studies are likewise indicated on methods for the prevention of radiation injuries. These include:

(1) Methods of physical detection of external radiation by the development of sensitive direct reading instruments capable of the detection of amounts of radiation well below those necessary for demonstrable injury to the animal subjects.

(2) Methods for the determination of harmful amounts of radioactive dusts and gases in air, in water and the like. Many radioactive materials like radium are deposited in the body and in such locations produce injury to tissue. Methods based on the determination of dangerous amounts of these substances by examination of the excreta and direct measurements of the body itself are necessary.

E. Protective Measures. Studies on the efficiency of shielding against radioactive materials, the efficiency of exhaust and ventilating systems against dangerous amounts of dusts, the development of protective clothing and devices, and the development of remote control processing methods have been extremely important in the Manhattan District protection program to date and will continue into the future.

F. The possible therapeusis of radiation damage by the use of replacement therapy for the damaged bodily elements, as well as the reduction in the exposure following deposition of radioactive materials in the body deserves considerable study. Replacement of the damaged hematopoetic elements destroyed by severe radiation exposure offers one possibility; detection and neutralization of unknown toxic substances produced by radiation and other such difficult problems deserve consistent and detailed study.

All the above studies are necessary on alpha, beta and gamma rays and neutrons of varying intensity. In addition, the radiation from the radioactive substances to be discussed has likewise to be considered. Also, the effects of acute and chronic exposure must be determined because of their dissimilarity.

II Hazards Due to Special Materials

For brevity it is preferable to discuss the potential toxicity of special materials by first indicating the type of study to be carried out, followed by the presentation of these materials on which studies have been necessary.

A. First, an actual determination of the toxicity of a substance must be made indicating how poisonous it may be in both acute and chronic exposure. In this way the toxic levels may be avoided in laboratory and plant environments.

(1) The mode of entrance into the body by ingestion, inhalation and skin absorption must be studied as different manifestations and degrees of toxicity may be produced by each route employed.

(2) A careful analysis must be made as to the character of the biological changes with the production of physiological, histopathological and biochemical evidences of damage incurred.

(3) The nature of these injuries and the mechanism by which they occur must likewise be studied inasmuch as this affords information as to the necessary protection and indicated therapy after exposure.

B. Preventative measures require study.

(1) The effectiveness of physical methods for the removal of hazardous dusts, reduction in skin contact and prevention of ingestion must be measured, and methods for accurate determination of such hazards must be developed and used. The use of certain chemicals, ointments, and the like as protective measures must be studied as to their efficiency.

(2) Protective devices such as respirators and clothing must be tested on required substances against which they will be used.

(3) Finally, appropriate investigation of therapeutic measures to be used in the treatment of both acute and chronic poisoning states should they occur in industrial exposure must be made.

Completion of all phases of the above program on a variety of substances provides complete information as to the medical aspects necessary to be considered in protection of the worker, prevention of injury and treatment of injury should it occur.

APPENDIX A (Cont'd.)

C. Substances on which studies of this type are necessary are:

(1) Uranium and its compounds

a. Uranium metal and its chemical compounds, oxide, nitrate, chloride, bromide, tetra and hexafluoride, sodium and ammonium sulfates.

b. Uranium chain of heavy metals

Uranium X1
Uranium X2
Radium
Polonium

c. Fission products of cleavage of U-235 and plutonium.

d. Artificial isotopes of uranium - 232, 234, etc.

(2) Thorium and its chain

(3) Plutonium

(4) Special Accessory Materials

a. Fluorocarbons
b. Fluorine
c. Beryllium
d. Others

III Production Hazards

The results of studies made on the materials discussed above are appli[illegible] for the prevention and control of industrial hazards arising in the large manufacturing areas where these materials are used in large amounts.

A. In the Electromagnetic and Diffusion Methods for the isolation of uranium 235 the major hazards are from the uranium compounds, the concentration of uranium X1 and X2, and the special accessory materials and by-products formed in the process of manufacture.

B. In the graphite pile where plutonium (239) is produced on a large scale, the hazards are from the alpha, beta and gamma rays, neutrons, the plutonium metal and its compounds, the various radioactive fission products resulting from the pile operation.

C. The chemical isolation of polonium following its formation in the pile incorporates hazards from alpha radiation following absorption into the body.

(5) Study of treatment of all immediate effects such as radiation, heat and blast.

(c) Preparation of pertinent information in proper form for use by catastrophe units in production areas.

D. Study of the medical aspects of plant programs aside from the determination of the effect of radiation and chemical toxicity, include additional information obtained from plant investigations as from:

(1) Clinical survey of all exposed personnel.

(2) Monitoring of hazards by special instruments and methods.

(3) Surveys of new types of graphite piles and production equipment.

IV Hazards of Atomic Catastrophe in Production Areas.

A. Immediate Effects

(1) Radiation - the radiation occurring at the time of the explosion coupled with blast and heat causes biological effects which may differ from those occurring following other acute known effects from gamma and neutron radiation, and demand study.

(2) Blast - the blast of atomic explosion is so intense and may have totally different types of shock waves, recoil waves with other unique biological effects which should be investigated.

(3) Heat - The intense burns from actinic type of radiation have not been studied. This also includes the combination effect of all three items in this group: blast, radiation and heat.

(B) Delayed Effects

(1) Protective Devices - study of methods of protection against the radioactivity deposited at the time of blast.

(2) Decontamination - methods of decontamination of soil and the like must be worked out for cleaning up active areas.

(3) Investigative Equipment - special equipment must be developed and tested for use in investigating bombed areas.

(4) Study of casualty effects - field study of fission clouds, possible injury to water supply, soil and the like, human damage by population surveys.

COPY

THE UNIVERSITY OF ROCHESTER
SCHOOL OF MEDICINE AND DENTISTRY
STRONG MEMORIAL HOSPITAL
Rochester, New York

January 30, 1947

AEC-729.5 (Univ of Rochester)

Mr. Carroll Wilson
General Manager
U.S. Atomic Commission
Washington 25, D. C.

Dear Mr. Wilson:

The opinion on Clinical Testing was requested of the Interim Medical Committee at its meeting January 23, 24, 1947. It is the opinion of this Committee that in the further study of health hazards and of the utilization of fissionable and radioactive, and other materials, final investigations by clinical testing of these materials will be necessary unde the proper and usual safeguards.

It is recommended that the legal department determine the financial and legal responsibility of the United States Atomic Energy Commission when such clinical investigations are carried out as part of approved programs financed by the Atomic Energy Commission and advise the proposed Health-Saf ety Division of its perogatives in this regard.

Sincerely yours,

STAFFORD L. WARREN, MD
Chairman, Interim Medical Com.
U.S. Atomic Energy Commission.

SLW:m
cc: Dr. F. A. Bryan
Dr. R. S. Stone
Med. Div, Oak Ridge

1029013

UNITED STATES
ATOMIC ENERGY COMMISSION
WASHINGTON 25, D. C.

March 7, 1947

TO: Mr. Edwin E. Huddleson, Jr.

FROM: John L. Burling

SUBJECT: Clinical Testing

This memorandum will record a conference between you, Dr. Stafford Warren, Major B. M. Brundage and the writer:

Dr. Warren and Major Brundage stated that under Manhattan Engineer District a program of employing radioisotopes in clinical testing had been commenced but that in January 1947 this matter had been brought to Colonel Nichols' attention. Colonel Nichols had orally expressed the desire to have the Medical Committee consider the program and, accordingly, he gave oral instructions that the distribution of the material for this purpose was to be suspended. On January 23 and January 24 the Committee met and did recommend a program of clinical testing. This recommendation is embodied in a letter to Mr. Wilson from Dr. Warren dated January 30, a copy of which is annexed to the original of this memorandum.

It is Major Brundage's understanding that the recommendation was not acted upon because Colonel Nichols had left Oak Ridge by the time it arrived. Currently, therefore, the suspension of the distribution of radioisotopes, which was put into effect to await the decision of the Committee, is continuing, although the Committee has formally recommended a program of clinical testing. Major Brundage stated that a formal program for clinical testing was being prepared and would be forwarded to Washington in about two weeks from the Research Division at Oak Ridge. Dr. Warren recommended that, pending the receipt of this program and its approval by the Commission, resumption of the release of radioisotopes for use by Commission research contractors on approved programs be continued under the procedures previously existing. You consulted with Mr. Wilson on the telephone and you gave legal approval to the recommendation, and Mr. Wilson accepted it.

The Legal Division expressed the view that in all clinical testing it would be necessary to make sure that the testing was being carried on in relation to a research program properly approved. We further expressed the view that it was most important that it be susceptible of proof that any

individual patient, prior to treatment, was in an understanding state of mind and that the nature of the treatment and possible risk involved be explained very clearly and that the patient express his willingness to receive the treatment. On Dr. Warren's recommendation, you authorized omission to obtain a written release but urged that in every case at least two doctors certify in writing to the patient's state of mind to the explanation furnished him and to his acceptance of the treatment.

It is contemplated that this memorandum will be initialed as a record of the interim authorization involved.

cc: Dr. Stafford Warren
Major B. M. Brundage

Attachment

CONFIDENTIAL

THIS DOCUMENT CONSISTS OF 2 PAGE(S)
UNITED STATES NUMBER 6 OF 21 COPIES, SERIES R
ATOMIC ENERGY COMMISSION
Washington, 25 DC

30 April 1947

Dr. Stafford L. Warren
University of California
405 Hilgard Avenue
West Los Angeles, California

Dear Dr. Warren:

This is to inform you that the Commission is going ahead with its plans to extend the medical research contracts of the University of Washington, Columbia University, Western Reserve University, the University of Rochester, and the University of California (at Los Angeles), in the amounts recommended by the budgetary subcommittee of the Interim Medical Advisory Committee, as recorded in your letter to me dated April 7, 1947.

It is the hope of the Commission that such extensions of the contracts will provide a sound basis for continuing the medical research essential to the Commission's activities, pending a fuller review by the Commission of the scope of the medical program. The Commission also hopes to strengthen the position of the Universities to attract personnel of high calibre to the medical research work, by authorizing them, with the approval of the Commission, to enter into contracts of employment with key personnel for periods up to three years.

The Commission is entirely sympathetic with the view of your Committee that research personnel engaged in medical projects should be encouraged to exercise their own initiative and should be given an opportunity to devote part of their time to pursuing lines of research which appear fruitful to them, even though not immediately related to specific items in the approved program for the particular project. Accordingly, the Commission is authorizing its Area Managers to approve such research, up to twenty per cent of the time of the research personnel engaged on such medical projects. When such approval is given, the Director of the medical project will be required to certify to the Commission (1) that the research is useful and is not outside the general scope of the Commission's research interests, and (2) that the research will not unduly interfere with the progress of the work on the approved program at the project. The Director also will be required to indicate separately in his reports to the Commission what research has been done under this authorization.

CONFIDENTIAL

It is understood that your Committee has recommended a program for obtaining medical data of interest to the Commission in the course of treatment of patients, which may involve clinical testing. The Commission wishes to make clear to your Committee its understanding of the program which is being approved. The Commission understands that in the course of the approved program:

a. treatment (which may involve clinical testing) will be administered to a patient only when there is expectation that it may have therapeutic effect;

b. the decision as to the advisability of the treatment will be made by the doctor concerned.

The Commission does not intend to influence in any way the exercise of judgment by the doctor as to the administration of any particular treatment authorized under the approved program. Indeed, from the discussion at the meetings of April 3-5, it seemed evident to me that doctors would not allow their judgment on this matter to be influenced by anyone.

In any such clinical testing, the Commission continues to request that the same procedure be followed which was agreed upon early in March. That procedure contemplated that it should be susceptible of proof from official records that, prior to treatment, each individual patient, being in an understanding state of mind, was clearly informed of the nature of the treatment and its possible effects, and expressed his willingness to receive the treatment. In view of your recommendation, the Commission does not request that written releases be obtained in such cases, but it does request that in every case at least two doctors should certify in writing (made part of an official record) to the patient's understanding state of mind, to the explanation furnished him, and to his willingness to accept the treatment.

The Commission is interested in exploring the possibility of starting various types of training programs along the lines recommended by your Committee. It is suggested that there should be submitted in writing detailed proposals for training programs, which do not go beyond the limits of what is now practicable.

Sincerely yours,

s/Carroll L. Wilson

t/Carroll L. Wilson
General Manager

UNIVERSITY OF CALIFORNIA
815 South Hill Street
Room 309
LOS ANGELES 24, CALIFORNIA

May 12, 1947

AEC - 730 (Rev.)

Maj B. M. Brundage
Chief, Medical Division
U. S. Atomic Energy Commission
P. O. Box E
Oak Ridge, Tennessee

Dear Maj Brundage:

Transmitted herewith for your information and files is a copy of a letter from Mr. Carroll Wilson to Dr. Stafford L. Warren.

The provisions indicated in paragraphs one and two will come into operation only where authorized specifically by contractual arrangements between the Commission and the Contractor.

Mr. Wilson's office has advised us that all Area Managers will be notified by the Washington Office concerning the contents of his letter.

The last paragraph of Mr. Wilson's letter suggests that plans be formulated for various types of training programs. It is requested that a tentative training program be forwarded to this office at your earliest convenience so that it may be correlated with the overall health-physics programs.

Sincerely yours,

Robert J. Buettner

Robert J. Buettner
Assistant to Chairman
Interim Medical Advisory Committee

RJB:m
Encl: Ltr dtd 30 Apr 47
from Mr. Wilson

1029019

Informat- from chart of Elmer Allen obtained on 4-18-74 at UC Record Center in Richmond

IC3

Elmer Allen - Unemployed

Dr. Lloyd Timbo 1304 Franklin St.; Oakland

Injury Sept 46

Referred to Dr. Carter as industrial. H. E. Carter, M.D. to transfer to County Hosp.

R. Bellamy in 8 wks. clinic recommends admission

Biopsy - called bone cyst.

Destructive lesion in lt. femoral condyle on x-ray.

R. J. Sherman was radiologist

Admitted 7-13.

Incorrect month Note on 5/16/47

Pt very comfortable and cheerful. A very cooperative pt. does move well.

R. Muller

Previous note 7/15/47

Incorrect month 5/17/47 X-ray scout films negative for any evidence of metastases. Amputation postponed until Monday in order to have radioactive tracer substances prepared (Plutonium) and standardized. Pt. will have tumor uptake studies done.

Muller

Incorrect month 5/18/47 Cast split down medial side. Some throbbing pain but no other discomfort. To surgery Monday. Hbg 92%, WBC 7,300

R. Muller

Cast removed for tracer injection.

0002681

Elmer Allen Chart

2

7-18-47 3:30 PM

The experimental nature of the intramuscular injection of the radioactive tracer sample was explained to the patient, who agreed on the procedure. The pt. was in fully oriented and in sane mind. Injection was given into the gastrocnemius muscle of left leg and the area marked with circle. Injection made at center of circle. Needle depth = 2 cm. No blood appeared on aspiration and no bleeding after removal of needle.

At explanation of the procedure to the patient and assisting in procedure were -

Miss Mary Wootton R.N.

Dr. Donald F. Bellamy

Dr. Ray Mullens

Dr. B. V. Low-Beer

Signatures here.

7-18-47 10:00 PM. No pain or discomfort whatsoever following injection.

R. Muller

7-21-47 Amputation

0002b82

Elmer Albert
3

Discharge note
7-7-47

Dx
1. Osteomyxochondrosarcoma of left femur - distal condyle.
2. R/ lues

Ray Mueller

[redacted]

707234

[redacted] September 28

[redacted]

[redacted]

SUBJECT: ABCC [redacted]

It is the desire of this office to present certain questions of medical policy to the Advisory Board on Medical and Public Health Problems for consideration. In view of the extremely important relationship of the medical program and health protection to many of the Commission activities, it is important to obtain basic medical policy decisions as rapidly as possible. The degree of success which the Commission's program attains may well depend in a large measure on the adequacy and soundness of its medical and biological program.

Accordingly, the following questions are submitted for review and approval with the request that they be transmitted to the Advisory Board on Medical and Public Health for consideration at their next meeting, October 31, 1947.

Dr. Albert R. Dolland, Jr., Acting Medical Advisor of the Oak Ridge Directed Operations, will be present in Washington on October 30th and will be available to provide the Board with further information if they so desire.

[redacted] the Biological Research Department at Clinton Laboratories, Oak Ridge, Tennessee, under the technical direction of Dr. [redacted], desires to establish a large long-term fundamental biological research program. Many phases of this program are already under way. However, very little so-called "programmed" biological research is being conducted, although there still are numerous problems requiring almost immediate answers. Apparently, it was the opinion of the Medical Board of Review which met last June that basic research of a non-classified nature should be done at the universities, and facilities such as there are available at Clinton Laboratories be utilized for whatever classified "programmed" investigation is necessary. Therefore, it becomes desirable to obtain a clear delineation of the type of work which should be conducted at Clinton Laboratories. Specifically, is there justification for a large comprehensive fundamental investigative program of non-classified subjects which do not at present directly relate to the many problems which confront the Commission, or should some of this fundamental work be referred outside the Commission as time or by use the Clinton facilities to initiate such [redacted] be done elsewhere?

[redacted]

Ridge Operations Office
REPOSITO... —
COLLECTION (RHTG) Classified Docs 1944-1994
Records Holding Area - Bldg 2714-H Vault,
BOX No. Box - RHA 11240-7 2 of 3
FOLDER None

Classification Changed to UNCLASSIFIED
By Authority of Classification Authority
By M.R. THESEN ANALYSIS CORP Date

1020777

Carroll L. Wilson

J. C. Franklin

MEDICAL POLICY

SUBJECT: ABCC

September

b. Subject to the approval of the Medical Director of the Atomic Energy Commission and the Advisory Board on Biology and Medicine, can the Medical Adviser of the Oak Ridge Directed Operations initiate "programatic" research at facilities within his area or with universities within his general geographic region?

c. What is the relationship of the Atomic Energy Commission Medical Division to the Isotopes Branch and the medical and biological aspects of the isotope distribution program?

(1) Will allocations for human administration be subject to medical review and what control will be exercised?

(2) What responsibilities does the Atomic Energy Commission bear for the human administration of isotopes (a) by private physicians and medical institutions outside the Project, and (b) by physicians within the Project? Latter category includes contractors personnel employed by Atomic Energy Commission funds (indirectly) to perform tracer research, some of which is of no importance to the agencies who pay the patients. Declare the criteria for future human tracer research?

Critique of human tracer research?

(3) What responsibilities does the Atomic Energy Commission bear for the safe handling by the recipient of the non-hazardous radioisotopes?

(4) What responsibilities does the Atomic Energy Commission bear for radioactive waste disposal outside the Project?

Declassification of medical and biological documents has become a considerable task. All researchers are anxious to have their work appear in the journals as soon as possible. When critical process steps or materials are involved the problem is greatly simplified, since all must abide by security. However, there are a large number of papers which do not violate security, but do cause considerable concern to the Atomic Energy Commission Intrance Branch and may well compromise the public prestige and best interests of the Commission.

1020778

CONFIDENTIAL

[redacted]

[redacted] September 5,

J. C. Franklin

[redacted]

[redacted]

Papers referring to levels of soil and water contamination surrounding Atomic Energy Commission installations, idle speculation on the future genetic effects of radiation and papers dealing with potential process hazards to employees are definitely prejudicial to the best interests of the Government. Every such release is reflected in an increase in insurance claims, increased difficulty in labor relations and adverse public sentiment. Therefore, it is requested that the Advisory Board on Biology and Medicine render an opinion or statement of consistent criteria for declassification of such documents. A similar problem arises in the declassification of medical papers on human contamination experiments done to date. Again many of these radioactive agents have been of no immediate value to the patient but rather a much needed opportunity for tracer research. Precedents are important and declassification criteria are requested.

What is the relationship between the Atomic Energy Commission Medical Division and the U. S. Public Health Service with respect to radioactive waste disposal and water and soil contamination? Will these problems under Public Law 725 remain primarily the responsibility of the Atomic Energy Commission?

J. C. Franklin

[redacted]

1020779

[redacted]

102

October 8, 1947

70713

To: Advisory Board on Medicine and Biology. [redacted]

Subject: MEDICAL POLICY.

It is the desire of the Medical Advisor's Office of the Oak Ridge Directed Operations to present certain matters of medical policy to the Advisory Board on Biology and Medicine for their consideration. In view of the extremely important relationship of health protection and the medical program to practically all of the Commission activities, and in a larger sense to national welfare, it is imperative to obtain basic medical policy decisions as rapidly as possible. The degree of success which the Commission's program attains may well depend in a large measure on the adequacy and soundness of its medical, health-physics and biological programs.

Accordingly, the following questions and tentative solutions are submitted for your review and expression of opinion.

Dr. Albert H. Holland, Jr., Acting Medical Advisor of the Oak Ridge Directed Operations, will be available for subsequent meetings of your Board to provide further information if you so desire.

a. There are approximately twelve cooperating universities participating in the Oak Ridge Institute of Nuclear Studies, which is a group established under the laws of the State of Tennessee to conduct fundamental research using the facilities available at Clinton National Laboratories. Although these facilities are necessary for much of the biological research work, a great deal of other work can be performed at the individual universities. Many competent qualified scientists

[redacted]

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from these universities have applied through this office for funds to conduct various problems in biochemical, medical and biological research. Some of these suggested researches are extremely pertinent to the activities of the Commission, as for example, Dr. Alfred Chanutin at the University of Virginia Biochemical Laboratory wishes to establish a program for the electrophoretic study of plasma proteins following irradiation. If in his studies he can establish a constant pattern change which can be correlated with radiation exposure, we will then possess a new diagnostic method which can readily be used in the protection of our personnel throughout the atomic industry. This type of problem, while fundamental in nature, can also be considered as applied or "programatic" research, since it is intended to attempt to provide us with a definite answer to an extremely pertinent problem.

Accordingly, the question arises as to whether or not a regional Medical Advisor can initiate fundamental and/or "programatic" research at facilities within his area or with universities within his general geographic region? It is apparent that each Medical Advisor has a more intimate knowledge of the problems within his area; and therefore it seems desirable, subject to the approval of the Atomic Energy Commission Medical Director and the Advisory Board on Biology and Medicine, that he have the authority to negotiate with universities within his region for the express purpose of conducting both fundamental and "programatic" research.

[redacted]

b. A second problem arises when one considers what responsibilities the Atomic Energy Commission bears for the human administration of isotopes. This question can be subdivided into two phases: (1) When the materials are administered by private physicians and institutions outside the Project and (2) when given by physicians and researchers within the Project. This latter category includes contractors' personnel employing Atomic Energy Commission funds (indirectly) to perform tracer research, some of which is of no immediate therapeutic value to the patient. It therefore becomes desirable to establish acceptable medico-legal criteria for future human tracer research.

Careful consideration of this problem seems to indicate that once a recipient has been deemed "qualified" by the Isotope Branch and their advisory committees to receive and use radio-isotopes, the Commission bears little if any responsibility for human administration. Past medico-legal experience provides numerous instances of claims and suits againstmedical institutions for the use of experimental drugs. In practically every case the physician involved has taken the sole responsibility and therefore may or may not be guilty of malpractice, but the institution is exonerated. This analogy might well apply to our present problem.

The second part of the question is more difficult since much of our research is motivated by human application and human effects. If the expressed opinion of the Medical Board of Revie which convened last June, is accepted in establishing criteria

for human administration, then obviously a great deal of our present human tracer studies must be discontinued. The pertinent facts of the case, pro and con, seem to be these: Pro -

(1) Tracer research is fundamental to toxicity studies.

(2) The adequacy of the health protection which we afford our present employees may in a large measure depend upon information obtained using tracer techniques.

(3) New and improved medical applications can only be developed through careful experimental and clinical trial.

(4) Tracer techniques are inherent in the radioisotope distribution program.

Con -

(1) Moral, ethical and medico-legal objections to the administration of radioactive materials without the patient's knowledge or consent.

(2) There is perhaps a greater responsibility if a federal agency condones human guinea pig experimentation.

(3) Publication of such researches in some instances will compromise the best interests of the Atomic Energy Commission.

(4) Publication of experiments done by Atomic Energy Commission contractors' personnel may frequently be the source of litigation and be prejudicial to the proper functioning of the Atomic Energy Commission Insurance Branch.

c. The radioisotope distribution program is increasing in scope very rapidly. As a result certain questions arise for consideration to determine:

(1) What part the Atomic Energy Commission Medical Division will

play in the isotope program?

(2) What responsibilities does the Atomic Energy Commission bear for the safe handling by the recipient for the more hazardous isotopes?

(3) What responsibilities does the Atomic Energy Commission bear for radioactive waste disposal?

(4) What part, if any, should the Atomic Energy Commission take with respect to cyclotron produced isotopes at the various universities throughout the country?

Answers to the above questions cannot immediately be set forth. However, the following comments appear in order:

It is felt that the Atomic Energy Commission Medical Division should probably bear complete responsibility for all of the medical and health-physics phases of the Commission's activities. The medical and health aspects of the isotope program therefore is a subject of some concern to the Medical Director. The establishment of broad general policies of personnel protection, codes, and other related information may well fall within the scope of the Medical Division's activities.

With respect to safe handling of the more hazardous isotopes, as for example, Strontium 90, Calcium 45 and Carbon 14, many factors arise which increase the difficulty of solution. These are listed below:

(1) Under the Atomic Energy Act does the Commission retain moral responsibility for the application of these substances?

(2) How can the Atomic Energy Commission properly enforce safe handling?

1019711

(3) The U. S. Public Health Service has no legal authority within state boundaries and therefore can only act in an advisory capacity. Further, there does not appear to be a sufficient number of qualified men to initiate such a Public Health service.

(4) State Public Health officers do have, in most instances, sufficient legal authority to enforce safe handling. However, few men are qualified at the present time to assume this responsibility.

(5) The Advisory Field Service of the Isotopes Branch provides "in the field" free consultation. A number of isotope recipients have availed themselves of this service. However, suggestions or recommendations requiring the expenditure of money for laboratory design in the interest of safe practice are not always received in a cordial manner.

Radioisotopes with a short half-life, such as Phosphorus, P^{32} and I^{131}, do not present a severe hazard in most cases. However, some substances may be of primary concern to an entire community if handled improperly. Some system of control is vital if extensive use of these substances is contemplated.

Intimately associated with the above problem is the question of radioactive waste disposal. As you no doubt are aware, many suggestions have been proposed by various people. Some of these are:

(1) Disposal at sea.

(2) Disposal by burial.

(3) Storage in vaults until decay has progressed to safe limits

(4) A system of garbage can collections and subsequent burial in federal burial grounds.

(5) Sealing the more hazardous contaminated wastes in suitable

containers and dispatching them by interplanetary rockets out into space.

While some of these suggestions appear somewhat extreme and others appear quite reasonable, numerous problems arise concerning waste disposal. Ground burial is at present in use at some installations. However, ground water and soil contamination and subsequent selective absorption by various plants and animal organisms is a serious objection to this method of disposal. Burial at sea is not without some hazard when one considers such a program extending over a long number of years.

Numerous isotope purchasers receive material which is not suitable for dilution and disposal in city sewage systems. Therefore consideration must be given as to what responsibilities we bear with respect to:

(1) Radioactive waste disposal.

(2) Establishment of criteria for disposal.

(3) Desired methods of enforcement, if any.

With respect to the cyclotron produced isotopes at the various universities and research institutions throughout the United States it might be desirable to have the same safety codes and personnel protection measures adopted. If cyclotron produced isotopes were to be purchased, distributed and handled at will throughout the United States, the efforts of the Commission to maintain safe practices may be seriously handicapped. Obviously, this is a very delicate question for we do not wish in any way to encroach upon the scientific liberty of free institutions.

d. Declassification of medical and biological documents has become a considerable task. All researchers are anxious to have their work appear in the journals as soon as possible. When critical process steps or materials are involved the problem is greatly simplified, since all must abide by security. However, there a large number of papers which do not violate security, but do cause considerable concern to the Atomic Energy Commission Insurance Branch and may well compromise the public prestige and best interests of the Commission.

Papers referring to levels of soil and water contamination surrounding Atomic Energy Commission installations, idle speculation on the future genetic effects of radiation and papers dealing with potential process hazards to employees are definitely prejudicial to the best interests of the government. Every such release is reflected in an increase in insurance claims, increased difficulty in labor relations and adverse public sentiment

Following consultation with the Atomic Energy Commission Insurance Branch, the following declassification criteria appears desirable. If specific locations or activities of the Atomic Energy Commission and/or its contractors are closely associated with statements and information which would invite or tend to encourage claims against the Atomic Energy Commission or its contractors, such portions of articles to be published should be reworded or deleted. The effective establishment of this policy necessitates review by the Atomic Energy Commission Insurance Branch, as well as by the Medical Division, prior to declassification.

In summary, it should be pointed out that this brief resume has not attempted to comprehensively present all of the problems which exist. It was deemed advisable, however, to set forth some of the major questions for your consideration. Even in the presentation of these major problems, no pretext is made for completeness. However, an effort was made to bring out the salient points in each instance. Primarily, the objective has been to call attention to those issues which appear to be fundamental to the establishment of a sound, progressive, coordinated medical and biological program for the Atomic Energy Commission.

[redacted] document consists of 12 pages
Copy No. 22 of 21 Series a

Copy of agenda of meeting in folder marked Agendas - ACBM

[redacted] R E T

corrected copy

DRAFT MINUTES

ADVISORY COMMITTEE FOR BIOLOGY AND MEDICINE

SECOND MEETING

Held At

Atomic Energy Commission Building

1901 Constitution Avenue

Washington, D. C.

October 11, 1947

[redacted]

The Committee discussed various aspects of the training program as summarized during the morning session. It was agreed that considerably more study would be needed on the many phases of the problem before a definite policy could be recommended to the Commission. Dr. Gregg requested each committee member to study the problem and prepare an opinion on the matter. Dr. Gregg proposed that these opinions be forwarded to him and he would assemble them for consideration at the next meeting.

Memorandum on Medical Policy

A memorandum addressed to the Committee, dated October 8, 1947 on the subject of medical policy from Dr. Albert Holland, Jr., Acting Medical Advisor, Oak Ridge Office of Directed Operations, was read. The memorandum brought up a number of important questions on medical policy related to health protection, medical research, human experimentation, the relationship of the Medical Division to the isotopes program, the problem of waste disposal of radioactive materials, and questions on declassifications of medical and biological reports. The Committee discussed the memorandum in general and expressed the desire to give the matter more study.

Letters of Interest

Letters of interest to the Committee, including research proposals by Captain C. W. Shilling (MC) USN on projects sponsored by the Office of Naval Research, and a letter from Dr. C. P. Rhoads, addressed to Mr. Lewis L. Strauss were discussed. Due to the number of projects cited in Captain Shilling's letter,

Dr. Gregg stated that he would acknowledge the letter and hold it for analysis by Dr. Warren and discussion at the next meeting.

A letter from Dr. Robert Stone, addressed to Mr. Wilson dated September 18, on declassification of biological and medical papers was read to the Committee. Dr. Stone's letter raised the question of releasing classified papers containing certain information on human experimentation with radioisotopes conducted within the AEC research program. The Committee agreed that the problem was covered by the recommendations of the Medical Board of Review and that papers on this subject should remain classified unless the stipulated conditions laid down by the Board of Review were complied with.

Third Meeting

The Committee agreed that the next meeting would be held in the Commission Building on Friday, November 7, 1947.

November 7th

The meeting adjourned at 6:00 P.M.

WAR DEPARTMENT
OFFICE OF THE SURGEON GENERAL
ARMY EPIDEMIOLOGICAL BOARD
UNITED STATES ARMY

OFFICE OF THE PRESIDENT
333 CEDAR STREET
NEW HAVEN, CONN.

Protection of Research Project Volunteers

Col. Frank L. Bauer Army Med. Res. & Development Board, SGO, Room 2C480	Legal Office, SGO Rm 2B520	23 Oct. 47	RJO/mf 74575

1. There is nothing in the Medical Department standard research and development contract which would require the Government to reimburse the contractor for a payment to a prisoner as compensation for injury resulting from participation in a research project. This is true whether the payment be made voluntarily by the contractor or as the result of a possible suit for damages. Although the contractor might be reimbursed under the special costs article for such payment I would consider it inadvisable to do so.

2. The question of reimbursing the contractor for payment of the premium on a disability policy on a prisoner during the experiment, was submitted to the Contract Insurance Branch, Office of the Chief of Finance. They advised that there was no authority for taking out such a policy and it would not be approved. They further stated that they discussed the question of such coverage with a private underwriter and were advised that the cost would be prohibitive.

3. This office, accordingly, recommends that Dr. Stokes be advised to protect himself, the State of New Jersey, and the Government, by means of the usual waiver if such action has not already been taken. This office will supply the necessary form upon request.

Robert J. O'Connor
Lt. Colonel, JAGD,
Chief, Legal Office

Incl. Ltr, 15 Oct. 47, fr Dr. Stokes
to Col. Stone

COPIED: 12/2/94
RECORD GROUP: #334
ENTRY: #14
FILE: Commission on Liver Diseases – Human Volunteers for Hepatitis Studies – Feb 1945 on
NOTE: ENCLOSURE NOT IN FILE

[redacted]

5 NOV 194

Dr. Robert S. Stone
University of California
Medical School
The Medical Center
San Francisco 22, California

CONFIRMED TO BE UNCLASSIFIED
BY AUTHORITY OF DOE/OC
Kahn 4-17-89
REVIEWED BY DATE
By: DICK KOOGLE 10-18-89

Dear Dr. Stone:

Your letter of September 18 regarding the declassification of biological and medical papers was read at the October 11 meeting of the Advisory Committee on Biology and Medicine. The Committee reaffirmed the stand of the Medical Board of Review, which met in June, and considers the matter of human experimentation classified where the conditions cited below were not complied with. For your information, the following is quoted from the preliminary unpublished and restricted draft of the report read to the Commissioners:

"The atmosphere of secrecy and suppression makes one aspect of the medical work of the Commission especially vulnerable to criticism. We therefore wish to record our approval of the position taken by the medical staff of the AEC in point of their studies of the substances dangerous to human life. We believe that no substances known to be, or suspected of being, poisonous or harmful should be given to human beings unless all of the following conditions be fully met: (a) that a reasonable hope exists that the administration of such a substance will improve the condition of the patient, (b) that the patient give his complete and informed consent in writing, and (c) that the responsible nearest of kin give in writing a similarly complete and informed consent, revocable at any time during the course of such treatment.

"Were it not for the extreme value and pressure for securing reliable information on the limits of human tolerance of radioactive substances there would be no need for explicit reference to this subject. We wish to see immediate and steady increase in this gravely important subject of human tolerance of radioactivity, but we believe that since secrecy must of necessity mark much of the medical research supported by the federally-sponsored AEC, particular care must be taken in all matters that under other circumstances would be open to investigation and publicity."

[redacted]

We trust that this information will assist you in evaluating this problem.

Your continued interest and support in our biological, medical and health physics program is deeply appreciated.

Sincerely yours,

Carroll L. Wilson
General Manager

Copy No. 1 Addressee
2 Mr. Wilson
3 Mr. Derry
4 Mr. Volpe
5 Dr. Fidler
6 Medical Director
7 Major Dauer
8 File

UNITED STATES
ATOMIC ENERGY COMMISSION
WASHINGTON 25, D. C.

5 NOV 194[illegible]

Dr. Alan Gregg, Director
for Medical Sciences
Rockefeller Foundation
Room 5500
49 West 49th Street
New York 20, New York

Dear Dr. Gregg:

I want to thank you for your letter of October 14 concerning the questions raised by Dr. Stone in his letter to me of September 18 regarding declassification of biological and medical papers containing information on the experimental use of radioisotopes in human beings conducted under AEC sponsorship.

I have checked the unpublished and restricted draft of the report of the Board of Review and note that their attitude was clearly stated on this problem. Accordingly, I agree with you that it is not necessary for the Advisory Committee for Biology and Medicine to make a further statement on this subject.

My reply to Dr. Stone included an extract of the Board of Review remarks. I am sure that this information will assist Dr. Stone in evaluating the present problem and inform him as to the conditions that must be met in future experiments.

Sincerely yours,

Carroll L. Wilson
General Manager

cc: Mr. Wilson
Mr. Derry
Mr. Volpe
Dr. Fidler
Medical Director
Major Dauer

AHH/ds

65

J. C. Franklin, Manager — November 7, 1947

Albert H. Holland, Jr., M.D., Acting Medical Advisor

MEDICAL AND OPERATIONAL POLICY DECISIONS

SYMBOL: AECT

Submitted herewith is a brief survey of the problems of both medical and operational policy which are presented for your consideration by this office.

1. The acquisition of acceptable personnel is extremely difficult. Existing Civil Service criteria do not adequately provide for some of the highly specialized technical fields which are peculiar to the Atomic Energy Commission. Further, the Civil Service pay scale cannot compete with industrial pay scales. Therefore, in any one instance an individual with a given amount of experience is usually entitled to less financial remuneration if he accepts federal employment. This is an unfortunate situation since the Atomic Energy Commission contracts advisory and supervisory services to its contractors, and therefore should be equipped with the best available personnel rather than the reverse.

2. For some time there has been a feeling among the health-physics groups on the Project that they should not be within the scope of the general medical and biological program. To date there has been no clear-cut delineation of this problem. GE Instruction 16 (Enclosure 1) is subject to considerable interpretations and provides opportunity for much reduplication of effort.

3. It is highly desirable to establish and maintain (see Enclosure 2) a uniform system of medical, biological and health-physics reports and distribution thereof. Essentially, this is a matter of national policy within the Atomic Energy Commission. The importance of such a system cannot be overemphasized particularly with respect to evaluation of illnesses alleged to be a result of occupation with the Atomic Energy Commission or its contractors. We have both a legal and moral responsibility which requires that we undertake adequate statistical surveys and interpret them in the light of our medical and biological research information. Such studies are mandatory if we expect to maintain the efficiency and success of our personnel protection program.

4. Many cases of illnesses arise which are alleged to be due to employment in the atomic industry, but require further medical study before a diagnosis of occupational disease can be established. It is highly desirable to have a central fund under the Director of the Division of Biology and Medicine from which all regional Medical Advisors could obtain the money necessary to conduct medical and research studies for cases which, in their opinions, require further study.

J. C. Franklin November 7, 1947

Albert H. Holland, Jr., M.D.

MEDICAL AND OPERATIONAL POLICY DECISIONS

SYMBOL: AEC

5. The Atomic Energy Commission holds many sub-contracts administratively within the ORDO but geographically lying outside the Oak Ridge area. The regional Medical Office is frequently called upon to visit such sub-contractors and review their medical and health programs particularly with respect to hazardous materials peculiar to the Commission's activities. Occasions arise when in the interest of safe operations and personnel protection expenditures of money must be contemplated in order to improve safe practices. It has never been clearly defined whether or not, for example, a company machining beryllium for AEC use can be requested or even directed to install more adequate ventilation. Management of course in most instances is perfectly willing to cooperate if we provide the funds. A definite policy is urgently needed so that we may determine where our responsibility for health and safety ceases. It should be borne in mind that a sub-contractor's employee can provide us with as much adverse publicity as an AEC employee.

6. The isotope distribution program is of primary importance to the Commission from a public relations viewpoint, but in a larger sense to the nation as well. The continuation of an active, forceful progressive isotope program cannot be overemphasized. However, there are many policy problems which arise from this activity. Questions such as the following still remain unanswered:

a. Does the Atomic Energy Commission's legal responsibility cease when an isotope has been delivered to the purchaser?

b. How far can moral responsibility be presumed to extend in this program?

c. Should the AEC undertake a large program and provide facilities for radioactive waste disposal for isotope recipients?

d. What part, if any, should the AEC assume with respect to cyclotron produced isotopes at the various universities throughout the country?

It may be desirable to have comparable safety codes and personnel protection measures adopted at the various universities and research institutions throughout the United States. The matter of effecting this is of some concern since if cyclotron produced isotopes can be purchased, distributed and handled at will throughout the United States, the efforts of the

J. C. Franklin, Manager — November 7, 1947

Albert H. Holland, Jr., M.D., Acting Medical Advisor

MEDICAL AND OPERATIONAL POLICY DECISIONS

SYMBOL: ABCT

Commission to maintain safe practices may be seriously handicapped. Obviously, this is a very delicate question for we do not wish in any way to encroach upon the scientific liberty of free institutions.

7. The establishment of an AEC sponsored training school in health-physics is urgently required. There are not sufficient men with adequate training to fill all of the needs of the Commission, its contractors, and outside agencies desiring to establish isotope research programs. It is strongly urged that one or two individuals be allowed to devote full time to training programs in health-physics and related subjects which purportedly would last approximately six to eight weeks. Most all of this instruction could take place outside of a restricted area and therefore representatives of industry, hospitals and research laboratories could be permitted to attend these training courses without divulgence of security to a large number of individuals and without necessitating lengthy clearances prior to instruction. The best assurance we have that our national isotope program will be conducted safely and wisely is to train personnel to recognize the radiation hazards presented by isotopic research.

Albert H. Holland, Jr., M.D.

2 Attachments:
1. GM Instruction 16
2. Cy memo to Legal Advisor fm Acting Medical Advisor, dtd 11/7/47.

Corrected Agenda

Stiv...

February 9, 1948

TO: Commissioners and Division Heads

FROM: Carroll L. Wilson, General Manager

SUBJECT: Meeting of the Advisory Committee for Biology and Medicine

The sixth meeting of the Advisory Committee for Biology and Medicine will be held February 14, 1948 at 9:30 A. M., at Washington, D. C.

Invitation is cordially extended to attend this meeting.

February 14, 1948

AGENDA

1. Correction of Minutes of December 13, 1947 Meeting:

The statement that the request for support of a research contract by Dr. Allen Moritz was approved, should be deleted from these minutes.

Gregg absent
Failla voted

OK

2. Additions to the Minutes of the Meeting of the Advisory Committee for Biology and Medicine held at Oak Ridge, Tennessee on December 13, 1947:

OK

In view of the suggestions made at the meeting of the Advisory Committee for Biology and Medicine on January 9, 1948 that a discussion be included in the Minutes of December 13, 1947 regarding the Isotope Distribution Committee, it is recommended that the following material be added to the Minutes of that meeting:

On October 30, 1947 it was announced that the Interim Advisory Committee on Isotope Distribution Policy and two subcommittees wished to resign. Accordingly, a new committee on Isotope Distribution was proposed by the Isotope Distribution Branch of the Atomic Energy Commission. Dr. Aebersold suggested

ORGANIZATION & MANAGEMENT 7

that the new committee be composed of the following persons who are closely associated with the use of isotopes:

Gioacchino Failla, Ph. D., Professor of Radiology, Columbia University Medical School, New York, New York.
Hymer L. Friedell, M. D., Director, Department of Radiology, Lakeside Hospital, Western Reserve University, Cleveland, Ohio.
A. H. Holland, Jr., M.D., Medical Advisor, Oak Ridge Directed Operations, Atomic Energy Commission.
J. C. Hamilton, M. D., Associate Professor, Medical Physics Department, University of California, Berkeley, California.
Joseph W. Kennedy, Ph. D., Chairman, Department of Chemistry, Washington University, St. Louis, Missouri.
Robley D. Evans, Ph. D., Professor of Physics, Massachusetts Institute of Technology, Cambridge, Massachusetts.
Robert F. Mehl, Ph. D., Director, Metals Research Laboratory, Carnegie Institute of Technology, Pittsburgh, Pennsylvania.
Austin M. Brues, M.D., Medical Director, Argonne National Laboratory, University of Chicago, Chicago, Illinois.
Paul C. Aebersold, Ph. D., Chief, Isotopes Division, as Secretary to the Committee and Liaison Representative of the Atomic Energy Commission.

It is suggested that Dr. Failla be appointed Chairman of the committee.

The proposed functions of this committee would be to aid the Commission in establishing new policies on the distribution of radioactive materials and to review from time to time existing policies. On specific isotope distribution problems it is hoped the members of the main committee would function as two sub-committees whose personnel and functions are given below.

Drs. Failla, Friedell and Holland should compose a Sub-committee on Human Applications who would review all initial requests for radioisotopes to be used experimentally or otherwise in human beings. Subsequent requests of a given user for the same purpose would not be reviewed.

Drs. Hamilton, Kennedy, Evans, Mehl and Brues should compose a Sub-committee on Allocations and Distribution who would review

doubtful requests for radioisotopes to be used in fundamental and applied research, the field of education, industrial applications, and commercial enterprises.

The Isotopes Division would assume responsibility for allocations of isotopes except for those cases specifically noted in paragraphs four and five. Because of the experience obtained during the past year and half of the program and the initiation of a field service on isotope techniques, the Division is well qualified to handle this responsibility. During the past few months it has been handling the routine work of allocation with a minimum of assistance by the advisory sub-committees. However, the Division has had to rely on the sub-committees for assistance on difficult decisions.

The above information has been drawn from a Staff Paper which was submitted to the Atomic Energy Commission by the Manager of the Oak Ridge Directed Operations. See also Addendum Minutes 13 Dec. 47.

3. Consideration of Minutes of the Meeting of January 9, 1948.

4. Research Projects:

Vice Chairman Goodpasture and the Interim Director of Biology and Medicine have recently discussed the general problem of support of research with the Acting General Manager. The Interim Director has recently conferred with Admiral Lee, Director of Office of Naval Research. The General Advisory Committee has outline its opinion on this problem and a statement from the members is enclosed.

(a) Contract between USAEC, Office of Santa Fe Directed Operations and Washington University, St. Louis, Missouri:

A research contract between the above-listed parties, negotiations for which were initiated last summer, has been entered into for the purpose of studies of nucleic acids, nucleoproteins, nucleotide and related organic phosphorus compounds in such a manner as to gain fundamental knowledge of the nature of disturbance of these compounds in organisms exposed to ionizing radiations. This project is supported to the extent of $29,500.

A second contract is for the construction of an ultraviolet spectrophotometer and an ultraviolet microscope for a study of the effect of ioni_ing radiation on cells. It is estimated that this work will cost $45,500. mention separate unit not available.

(b) Dr. Leonard B. Clark, Union College:

This is a request for support for a program of research on "The Biological Effect of High Voltage Radiation" using the facilities of the General Electric Company, Schenectady, New York. The work will involve a range of one million to one-hundred million volts as emitted by the hundred million volt betatron, with financing estimated for this work to be $29,500. There is only one other similar betatron.

RECOMMENDATION: It is recommended that the Advisory Committee for Biology and Medicine approve that the Office of Naval Research be notified that funds in the amount of $29,500 are available for one year beginning July 1, 1948 for the support of a research project at Union College in cooperation with General Electric Research Laboratory, Schenectady, New York, by Dr. Leonard B. Clark entitled "The Biological Effect of High Voltage Radiations." OK

Committee feels such an original idea should be encouraged.

(c) Dr. David Rapport, Tufts College Medical School:

This is a research project on "The Effects of Radiation on Reactions Associated with Growth." For many years this laboratory has worked on the catabolic aspects of metabolism, with support from the National Cancer Advisory Council and National Research Council. They have considered the effects of growth-influencing factors, chiefly hormonal, on these reactions. They have studied the capacity of the liver to synthesize alanine from pyruvic acid and a considerable number of similar reactions. They wish to determine the effects of radiation on such reactions in normal tissues and in tumors.

RECOMMENDATION: It is recommended that the Advisory Committee for Biology and Medicine approve that the Office of Naval Research be notified that funds in the amount of $15,000 are available for one year beginning July 1, 1948 for the support of a research project at Tufts College Medical School by Dr. David Rapport entitled "The Effects of Radiation on Reactions Associated with Growth."

O.K.

(d) Howard University - Dr. Herman Branson:

This department requests $11,400 to support studies in biochemistry ~~physics~~ at Howard University from 15 January 1948 through 15 January 1949. A program of investigation with radioactive and stable isotopes including a 60° Nier type mass spectrometer with the most recent refinements is projected. Studies will include investigations on phosphorus metabolism with P^{32}, determination of rate functions and metabolizing functions for biological systems by means of radioactive and stable isotopes and cooperative projects on iodine metabolism, cobalt metabolism and arsenic poisoning. The Office of

Naval Research is supporting this group to the extent of $6,800 for the program in mass spectrometry.

RECOMMENDATION: It is recommended that the Advisory Committee for Biology and Medicine approve that the Office of Naval Research be notified that funds in the amount of $11,400 are available for one year retroactive to 15 January 1948 for the support of research projects at Howard University by Dr. Herman Branson on Biophysics.

OK

(e) Dr. Louis Ridenour, University of Illinois:

This request is for a sum of $3,000 to support a project for the construction of a small radiocobalt applicator to be used in the irradiation of various types of small biological specimens. Such an applicator could be used in studying enzyme reactions, in split dose effects on mice and beans and as standard to test consistency of effects.

OK

RECOMMENDATION: It is recommended that the Advisory Committee for Biology and Medicine approve that the Office of Naval Research be notified that funds in the amount of $3,000 are available for one year beginning April 1, 1948 for the support of a research project at the University of Illinois under direction of Dr. Henry Quastler entitled "A Proposed Cobalt 60 Applicator for Radiobiology."

(f) Dr. Paul Hahn - Meharry Medical College:

This project is entitled "A Program for Treatment of Neoplasms by the Direct Infiltration of Radioactive Heavy Colloids."

Dr. Hahn has recently published several articles in which he reports encouraging results in treating various types of tumors including fibrosarcoma, epidermoid carcinoma and Hodgkin's Disease with direct infiltration of radioactive isotopes. Dr. Hahn's request is for $109,404.

RECOMMENDATION: It is recommended that the Advisory Committee for Biology and Medicine approve that the Office of Naval Research be notified that funds in the amount of $50,000 are available for one year beginning July 1, 1948 for the support of a research project at Meharry Medical College by Dr. Paul Hahn entitled "Radioactive Gold Colloids in Treatment of Neoplasms by Direct Infiltration." This approval is contingent upon the appointment of a medical advisory committee, from the Argonne Institute of Nuclear Studies, to supervise the medical aspects of the program. Safety instructions should be approved by ORI.

(g) Massachusetts Institute of Technology - Harvard Medical School:

Since 1940 there has been in progress a joint study using radio-isotopes by physicians of the Peter Bent Brigham Hospital and the Harvard Medical School and physicists at the Radioactivity Center of the Massachusetts Institute of Technology. This group has made many important contributions on the role of iron, zinc and other metals in the metabolism of human erythrocytes and leukocytes and it is also studying the alterations of these processes in blood dyscrasias. Recent developments emphasize the importance of zinc in the white blood cells in relation to leukemia. This group of physicians has requested that the Atomic Energy Commission assume support of their work by allocating $73,650. It was the desire of the Committee that this request be considered during the month and be acted upon at the February meeting of the Committee.

RECOMMENDATION: It is recommended that the Advisory Committee for Biology and Medicine approve that the Office of Naval Research be notified that funds in the amount of $73,650 are available for one year beginning July 1, 1948 for the combined program of Harvard University Medical School and Massachusetts Institute of Technology and Peter Bent Brigham Hospital on the "Certain Medical Aspects of Atomic Energy."

[redacted]

(h) Sloan-Kettering Institute - Dr. C. P. Rhoads:

This project desires to study the use of radioactive isotopes in the treatment of various thyroid states. Particular emphasis would be placed on hyper-function of the gland, neoplasms and conditions affecting iodine uptake.

RECOMMENDATION. It is recommended that the Advisory Committee for Biology and Medicine approve that the Office of Naval Research be notified that funds in the amount of ~~$[illegible]~~ are available for one year beginning April 1, 1948 for the support of research projects at Sloan-Kettering Institute by Dr. C. P. Rhoads entitled "Studies of Distribution of Isotopes in Therapy" ~~and "Tissue [illegible] Studies"~~.

OK

40,000

[redacted]

[redacted]

Complete study of biologic warfare
Cereal rusts
Late blight of potatoes
Curly top of sugar beets

Varieties of plants resistant, but new forms may come in - high degree of specificity.

Produce mutations by radiation.
Studies in genetics of pathogenicity.

Close liaison at highest level & close liaison ?

Nature of project
Confidence in man
Spinning inst.

Amended recommendation considered
OK

Deadline @ 2.45

Breakdown of amts from different subjects to Mem, Hdqtrs.
? Areas in which to spend funds.

~~[illegible]~~

1. Dollard + small group —
Allport

a) Organization civilian defense against A.E.

b) Advise A.E.C. with selling of the peace time aspects of A.E. — [illegible] + med. — [illegible] — [illegible]

Articles
Edits [illegible]
Formal infiltration of med curriculum. Deans — med. agencies.

(i) Michael Reese Hospital - Dr. Erich M.Uhlmann:

Dr.Uhlmann of this hospital has been investigating the use of an electron beam in 22-million electron volt betatron. They are anxious to build a 35-40 million electron volt betatron and study the fast electron produced by such a machine. In addition they are interested in a large research program on the biophysical approach to cancer therapy.

Declined

RECOMMENDATION: The correspondence from this hospital is enclosed and no recommendation is indicated at the present time.

(j) Washington University - Dr. James Nolan:

This project requests funds for support of a program to study the "Use of Gamma Ray Emitting Radioactive Isotopes in Colloidal Form as Therapeutic Agent in Carcinoma.

RECOMMENDATION: It is recommended that the Advisory Committee for Biology and Medicine approve that the Office of Naval Research be notified that funds in the amount of $9,800 are available for one year beginning July 1, 1948 for the support of a research project at Washington University by Dr. James Nolan entitled "Use of Gamma Ray Emitting Radioactive Isotopes in Colloidal Form as Therapeutic Agent in Carcinoma.

OK

(k) Dr. J. Levitt; Department of Botany, University of Missouri:

This request is for a small grant to support a problem on the trans-location of mineral substances in plants. This would include in what tissues they are moved, what the mechanism of movement is, and what relationship it has to other physiological processes. Movement would be followed with Geiger counters and would begin with radiophosphorus.

Dr. Levitt received his Ph. D. from McGill University and has worked on "Cold Resistance," "Cellular Physiology," and "Permeability." Studies at present are under way on the "Movement of Radioactive Isotopes in Plants" at institutions including Washington State College, Cornell University, Florida Experimental Station and University of California, Berkeley.-

RECOMMENDATION: It is recommended that the Advisory Committee for Biology and Medicine approve that the Office of Naval Research be notified that funds in the amount of $675 are available for one year beginning July 1, 1948 for the support of a research project at the University of Missouri by Dr. J. Levitt entitled "Trans-location of Mineral Substances in Plants." Subject to ~~approval~~ of University approval.

(l) Dr. Alfred Chanutin - University of Virginia:

Dr. Chanutin is Professor of Bio-chemistry at the University of Virginia and has been engaged in studies on the "Distribution and Chemical Changes of Proteins on the Plasma and Tissues in Normal and Pathological States in Research Animals and Human Beings." He is at present working on research contracts in the Chemical Corps of the United State Army and from the Office of Naval Research.

Dr. Chanutin proposes a study of the "Plasma and Tissue Protein Fractions" in animals and patients who have been exposed to varying doses of radiation for varying periods of time. The

work would be carried out originally on rats.

Dr. Stafford Warren at University of California, Los Angeles, has also proposed a program of study on "Plasma and Protein Fractions in Radiation." All available evidence on this program has not yet been activated.

RECOMMENDATION: It is recommended that the Advisory Committee for Biology and Medicine approve that the Office of Naval Research be notified that funds ~~in the amount~~ not to exceed of $25,000 are available for one year for the support of a research project at University of Virginia by Dr. Alfred Chanutin entitled "Plasma and Tissue Protein Fractions."

5. Technical Information and Publications:

At its last meeting the Advisory Committee considered preliminary discussions of the problem of dissemination of scientific information. Dr. A. Thompson, Chief of Technical Information Branch, Atomic Energy Commission, is available for discussion of this problem.

6. Programs in the Division of Biology and Medicine recently approved by the Atomic Energy Commission:

(a) Fellowship Program

(b) Cancer Research Program

7. The Use of Radioactive Materials for Military Purposes:

The Atomic Energy Commission has recently been informed of a projected program as a collaboration between the Division of Military Application and the Division of Biology and Medicine. This program has recently been considered and discussed by the General Advisory Committee. It is desired that the Advisory Committee for Biology and Medicine consider this program and submit such remarks or recommendations as are pertinent.

[redacted]

(6-a) Marine Biological Laboratory - Dr. Charles Packard:

A grant of $4,300 has just been made to the Marine Biological Laboratory by the Committee on Growth of the National Research Council to equip a radioactivity laboratory and to pay for the services of a technician during the coming summer.

A two-months course on radioactive isotopes will be given this summer consisting of lectures and demonstrations of interest particularly to biologists.

It seems desirable to provide some funds for summer fellowships to enable qualified young men and women to do some work in radiobiology under proper supervision, the primary objective being the experience and interest they would gain in this new field.

It is suggested that the stipend for each fellowship be ~~$500.~~ and ~~additional $300 per fellowship~~ be made available to pay for laboratory space, supplies, etc. when necessary.

The number of fellowships should not exceed six, amounting to $4,500. An additional sum of $800. should be provided for transportation charges for isotopes and unusual expenses in connection with the course on isotopes.

It is desirable that radioactive isotopes in reasonable amounts be supplied to the fellows free of charge for the work at the M. B. L.

The research problems to be undertaken by the fellows would involve:

A. Study of biological effects of radiation

B. Study of biological phenomena by means of radioisotopes

Fellows would be appointed by the Director of the M. B. L. (Dr. Packard) and the members of the Committee on Isotopes of M. B. L.

RECOMMENDATION: It is recommended that the Advisory Committee for Biology and Medicine approve the granting of funds to the Marine Biological Laboratory up to ~~$5,300.~~ for summer fellowships in Radiobiology and incidental expenses, for the summer of 1948.

5,300+

O K

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[redacted]

DOE ARCHIVES

8. Other Business:

(a) Letter from Dr. Cecil Watson

(b) Letter from Dr. Robert Stone

(c) Industrial Health and Safety Report

(d) The Commissioners are anxious to meet with the members of the Advisory Committee for Biology and Medicine to discuss certain phases of the program. If it is possible such a period will be arranged on February 14, 1948.

Mouse genetics - organic chemistry
Mr Lear - OK
Consultants
Stay Warren's letter
Public Relations report.

Carroll Wilson - ONR

COMMISSION ON VIRUS AND RICKETTSIAL DISEASES
333 CEDAR ST.
NEW HAVEN 11, CONN.

xxxxxxxxxxxxxxxxx

February 18, 1948

Dr. Joseph Stokes, Jr.
Children's Hospital
18th and Bainbridge Streets
Philadelphia 46, Pennsylvania

Dear Joe:

This is in reply to your hand written request for a comment from me re your letter to Dr. MacLeod dated 11 February on the subject of funds for the reimbursement for volunteer prisoners who may be sufficiently disabled as a result of their acquiring experimental hepatitis to prevent their full return to gainful occupation. This is an administrative question and if it were to be done, I presume that the amount of money to be set aside would have to be at least $50,000. The problem I presume is whether the Board would recommend that such money be held in reserve for such an emergency.

As to the second question relating to studies on humans which as you say raises a point of "ethics", I agree with your principles but believe the timing is not as opportune as it should be. Namely, that at this stage in the world situation one should proceed cautiously, until standards are set up by what ever body is in "authority". I am not sure just what the rules are but I understand that Dr. Ivy at the University of Illinois has been on some type of vigilance committee which has laid down certain principles about volunteers in order to protect this country from the critisms brought up in Germany during the Nürnberg trials. The Russians in Japan have also accused U.S. scientists of experimenting on humans. During the war we more or less made our own policies on this, but I am not sure that that is possible today and if there are to be official policies, I believe, we have to know them before any official statements could be made.

Yours sincerely,

John R. Paul, M.D.
Director

JRP:fd
cc: Col. Bauer
Dr. MacLeod

COPIED: 12/2/94
RECORD GROUP: #334
ENTRY: #14
FILE: Commission on Liver Diseases – Human Volunteers for Hepatitis Studies – Feb 1948 on

UNITED STATES
ATOMIC ENERGY COMMISSION

In Reply Refer To:
IE:SAL

709648

Oak Ridge, Tennessee
July 19, 1949

Dr. Hymer L. Friedell
Dr. G. Failla
Dr. Joseph G. Hamilton
~~Dr.~~ A. H. Holland

Subject: REVISED TENTATIV. MINUTES OF MARCH 13, 1949 MEETING OF SUBCOMMITTEE ON HUMAN APPLICATIONS OF COMMITTEE ON ISOTOPE DISTRIBUTION OF U. S. ATOMIC ENERGY COMMISSION, AEC BUILDING, WASHINGTON, D. C.

Gentlemen:

Enclosed is a copy of revised draft of the Tentative Minutes of March 13, 1949 Meeting of Subcommittee on Human Applications of Committee on Isotope Distribution of U. S. Atomic Energy Commission, AEC Building, Washington, D. C. This revision is based upon written comments received from Dr. Joseph G. Hamilton, Dr. G. Failla, and upon oral comments received from Dr. Hymer L. Friedell. No comments on the Tentative Minutes submitted April 29, 1949, were received from Dr. A. H. Holland.

You are requested to submit a letter of approval of this revised draft as quickly as possible so that the Isotopes Division can:

1. Prepare the circulars described in letter of April 26, 1949, from S. Allan Lough to the members of the Subcommittee.

2. Send a letter to the Atomic Energy Commission recommending:

   a. Acceptance of Dr. Hamilton's resignation and the appointment of Dr. Dr. Harold Copp as his successor.

   b. Appointment of a chairman of the Subcommittee on Human Applications to serve from July 1, 1949, to July 1, 1950.

Very truly yours,

S. Allan Lough

S. Allan Lough, Chief
Radioisotopes Branch
Isotopes Division
Oak Ridge Operations

Organization & Management 6
Human Applications

Encl.:
Minutes

LL10007

REPOSITORY NARA Attn: to Archives
COLLECTION RG 326-68A1096 OR-
BOX No #40 Division of Research
FOLDER Organization and Mgt
6 Meetings + Conferences - Human Applications

Subcommittee Members
April 29, 1949

This circular may be issued as a revision of Isotopes Division Circular E-35, a copy of which is enclosed.

A third circular will embrace the following items in the minutes:

III.A. Policy regarding field and industrial uses of long-lived radioisotopes.

III.D. Policy on level of activity that might be permitted in products and items sold to the public.

1. Emitters of beta particles.

2. Gamma emitters.

We shall welcome your comments on the tentative minutes.

Very truly yours,

S. Allan Lough, Chief
Radioisotopes Branch
Isotopes Division
Oak Ridge Operations

Encls.:
1. Cir. E-35
2. Minutes

2000778

REVISED

TENTATIVE MINUTES OF MARCH 13, 1949, MEETING OF

SUBCOMMITTEE ON HUMAN APPLICATION OF

COMMITTEE ON ISOTOPE DISTRIBUTION OF

U. S. ATOMIC ENERGY COMMISSION

AEC BUILDING, WASHINGTON, D. C.

The Subcommittee on Human Applications of the Atomic Energy Commission Committee on Isotope Distribution convened at 9:30 a.m., March 13, 1949, in Room 213 of the Atomic Energy Commission Building, Washington, D. C. Those present were Drs. Hymer L. Friedell, Chairman, G. Failla, and A. H. Holland. Dr. Joseph G. Hamilton was absent. Drs. Nathan H. Woodruff and S. Allan Lough were present as representatives of the Isotopes Division.

The Subcommittee established the following agenda:

I. Review of the minutes of the last meeting, March 22, 23, 1948.

II. Distribution of isotopes for cancer research.

III. Discussion of specific items pointed out by Dr. Woodruff in his letter of February 5, 1949.

A. Policy regarding field and industrial uses of long-lived materials.

B. Review of policy relative to allocations on supplementary requests.

1. Cases in which the quantities requested have been materially increased for the same purpose.

2. Cases in which the original allocation does not conform with the latest revised policies.

2000779

C. Review of action taken on application for human use of radioiron and formulation of a policy for future guidance.

D. Discussion of policy on level of activity that might be permitted in products and items sold to the public.

E. Clarification of policy on hospitalization and supervision of patients receiving radioisotopes through Atomic Energy Commission facilities. Attention was focused on this item by a statement occurring in "Experience with Radioactive Iodine in the Treatment of Hyperthyroidism" by George Crile, E. Perry McCullagh and Otto Glasser in Cleveland Clinic Quarterly 16: 1-7, 1949. The statement read:

> "3. Neither hospitalization nor supervision of the patient is required and the cost of treatment is less than that of thyroidectomy or prolonged medical treatment."

F. Use of radioisotopes in pregnancy and in normal children.

IV. Review of Violation of "Acceptance Terms".

V. Review of specific applications not yet acted upon by this Subcommittee.

VI. Revision of Form AEC-313.

VII. Development of method for replacement on some regular basis of members of the Subcommittee on Human Applications.

I. Review of the minutes of the last meeting, March 22, 23, 1948.

A. Consideration of use of radioisotopes in tracer studies in normal adult humans. The following remarks apply to beta and gamma emitters with a biological half-life of 20 days or less. These remarks are for general guidance but the Subcommittee on Human Applications will examine each case on its own merits.

Applicants who desire to use radioisotopes in normal adults should submit the results of animal experiments, or adequate references to the literature, concerning the following points.

1. Metabolism and distribution of the radiomaterial in the form administered.
2. The tissue of highest concentration and the relative concentration therein.
3. The relative concentrations in the tissue of interest and particularly radiosensitive tissues such as the gonads and hematopoietic system.
4. The biological half-life of the radioisotope in the tissue of highest concentration, the tissue of interest and the particularly radiosensitive tissues.

All tracer studies in normal humans must be approved by the local Radioisotopes Committee before consideration of the Application will be made by the Subcommittee on Human Applications.

The above statements apply to both Atomic Energy Commission and other installations.

B. Applications for use of radioisotopes in normal children will be given special scrutiny by the Subcommittee on Human Applications.

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C. Review of Policy with regard to long-lived radioisotopes.

1. In general, for isotopes with a biological half-life greater than 20 days, the dosage in the critical tissues should be such as to conform to the limitations stated by the National Committee on Radiation Protection. In special cases, however, the Subcommittee on Human Applications may permit the use of radioisotopes in higher dosages.

2. The Subcommittee on Human Applications feels that each request for use of a long-lived radioisotope in human subjects must be reviewed separately.

3. In the minutes of the initial meeting of the Interim Advisory Committee on Isotope Distribution Policy, held June 28, 1946, at Oak Ridge, the following statement appears on page 9.

"Carbon 14. The opinion was generally expressed that, even though the scarcity of C 14 is a major factor to be considered, the use of this material in a human being should not be sanctioned until its absorption and elimination properties is clearly demonstrated in animals. The very long half-life of the material makes caution desirable."

The Subcommittee on Human Applications feels that, in view of recently accumulated information, it is prepared to consider applications for use of certain C 14 compounds in humans. In arriving at this conclusion, the following papers were considered:

a. "The Fate of C 14 in the Tissues of Mice after Administration of C 14 Methyl-Labeled Glycine" By George L. Hardi, M. D., Radiation Laboratory and Division of Medical Physics, University of California, Berkeley, California. January 6, 1949.

b. Letter from John H. Lawrence, Donner Laboratory, University of California, February 18, 1949, which accompanied Hardi's paper, listed as "a", above.

c. "Report on Estimated Doses Delivered to Organs of Man by C 14 in Methyl-Labeled Glycine". By William Siri. This report is based on Hardi's paper, listed as "a", above.

d. "Studies on the Hazard Involved in Use of Carbon 14. I. Retention of Carbon from Labeled Sodium Bicarbonate". TECHNICAL REPORT NO. 1 to Office of Naval Research (Biophysics Branch, Medical Sciences Division) and Atomic Energy Commission, Division of Biology and Medicine. Contract N7onr-385, Task Order II, NR 171642. By Southern Research Institute, Birmingham, Alabama, March 28, 1949. 457-121-TI.

4. The Subcommittee asked that the Isotopes Division send to the members a complete re-statement of Allocation No. 2283 of tritium to Dr. John Lawrence. This statement will be prepared and sent out under separate cover. (Dispatched to the Subcommittee on Human Applications on March 25, 1949.)

D. It is recognized that there may be instances in which the disease from which a patient is suffering permits the administration of larger doses for investigative purposes. Applications for such uses of radioisotopes will be given special consideration by the Subcommittee providing:

1. Full responsibility for conduct of the work is assumed by a special committee of at least three competent physicians in the institution in which the work is to be done. This will not necessarily be the local Radioisotope Committee.

2. The subject has given his consent to the procedure.

3. There is no reasonable likelihood of producing manifest injury by the radioisotope to be employed.

II. Distribution of isotopes for cancer research.

A. Cancer research is interpreted to include the following:

1. Investigation of the basic aspects of normal and abnormal cellular growth.

2. The development and evaluation of therapeutic and diagnostic procedures for cancer and allied diseases.

B. The Subcommittee on Human Applications expresses confidence in the way the Isotopes Division is handling the allocation of Iodine 131, Phosphorus 32 and Sodium 24 for use in diagnosis, therapy and research in cancer and allied diseases.

C. Cobalt 60 needles.

The use of Cobalt 60 needles is not considered research by the Subcommittee on Human Applications unless the needles are of some unusual design or incorporate some unusual feature.

The National Cancer Institute has standards for determining those to whom radium needles might be lent. The Isotopes Division was asked to obtain these standards and to send them to the Subcommittee. The Subcommittee will then recommend a way to control the distribution of Cobalt 60 needles.

III. Discussion of specific items pointed out by Dr. Woodruff in his letter of February 8, 1949.

A. Policy regarding field and industrial uses of long-lived materials.

The Subcommittee's opinion is that consideration of requests for field and industrial uses of radioisotopes is primarily one of safety control accountability. Illustrative situations were reviewed as follows:

1. Cobalt 60 in nails to be used in wooden survey stakes. (Request No. 2380, U. S. Dept. of Interior, Bureau of Reclamation, Great Falls, Montana. Also Request No. 2373, Tracerlab, Inc.). In the use as proposed, the hazard was considered nil, but this application was rejected because of inadequate long-term control of the activity.
2. S 35 in the underground firing of coal mines. (Request No. 2895, cancelled). This proposal by the Southern Research Institute was considered safe under the conditions outlined.
3. Yttrium 90 in simulated plane crashes. (Request No. 2863). The National Advisory Committee on Aeronautics' proposal to use Y 90 stearate in labeling gasoline in simulated plane crashes was considered acceptable, providing the work would be done in an area sufficiently remote from human habitation. The proposal to conduct this work on the Cleveland Airport was disapproved.
4. The use of Cobalt 60 for standards (100 mc each) to calibrate field instruments of the Armed Services was briefly discussed. The Subcommittee on Human Applications felt that the use of Cobalt 60 in amounts of the order of 100 mc for standardization of instruments is reasonable. If and when the Armed Services

make such requests, a way should be found to provide the standards but without relaxation of safety rules.

B. Review of policy relative to allocations on supplementary requests for use in human subjects.

1. When greatly increased amounts are requested for the same purpose, as indicated on an earlier request, the decision as to whether the application can be approved will be left to the Isotopes Division. Such applications should be justified by:

   a) A commensurate increase in patient load.

   b) An expanded research program.

   c) Provision of adequate storage and handling facilities.

   d) Assurance that personnel protection and supervision are adequate for the larger amounts requested.

2. If the supplementary application includes a proposal which was formerly acceptable, but now conflicts with revised policies, it will not be approved. The applicant will be asked to revise his application to make it conform with current policies. This application will then be submitted to the Subcommittee on Human Applications for review and recommendation.

C. Review of action taken on applications for human use of radioiron and formulation of a policy for future guidance.

Dr. Holland was requested to work up data on the distribution of iron in the organism and to send a statement on this matter to the members of the Subcommittee on Human Applications for their use in

making calculations. The Subcommittee would then formulate a policy with regard to allocation of iron for human use.

D. Discussion of policy on level of activity that might be permitted in products and items sold to the public.

1. Emitters of beta particles.

Proposals to incorporate beta emitting radioisotopes in products offered for sale can be approved if (1) the activity is in insoluble form and incorporated permanently in inert material, and (2) the product produces no more radiation than 0.3 rep/wk at the surface. Dr. Holland suggested that a survey be made in the field to determine the actual background of radioactivity in industrial materials.

2. Gamma emitters.

Products containing gamma emitters must meet the conditions outlined above for beta emitters. In addition, when products are stored in warehouses, monitoring must be done to show that the radiation level is in accord with the regulations stated in the handbook on Safe Handling of Radioisotopes issued by the National Committee on Radiation Protection.

(See Section 1,(c),(2), p. 5).

E. Clarification of policy on hospitalization and supervision of patients receiving radioisotopes through Atomic Energy Commission facilities.

Dr. Crile's statement in the article referred to was discussed. The Subcommittee objected to the phrase "no supervision". It was felt that patients could appropriately be treated with radioactive iodine without hospitalization but that it was an overstatement to say that they did not require supervision. There was some objection to Dr. Crile's statement that the cost of treatment with radioiodine is low. Dr. Friedell felt that the present price is artificial and is lower than it should be, if cost of production were included. It was pointed out that the cost has been established by considering the radioiodine as a byproduct of pile operation and that on this basis the price may not be out of line. Dr. Failla remarked that, after all, the price considered by Dr. Crile is the price now.

F. Use of radioisotopes in pregnancy and in normal children.

1. Pregnancy.

The Subcommittee on Human Applications feels that the use of radioactive materials in all normal pregnancies should be strongly discouraged where no therapuetic benefit is to be derived.

2. Normal children.

In general the use of radioisotopes in normal children should be discouraged. However, the Subcommittee will consider proposals for use in important researches, provided the problem cannot be studied properly by other methods and provided the radiation dosage level in any tissue is low enough to be considered harmless. It

should be noted that in general the amount of radioactive material per kilogram of body weight must be smaller in children than that required for similar studies in the adult.

IV. Review of violation of "Acceptance Terms."

The Subcommittee reviewed the violation of the "Acceptance Terms" by Dr. F. C. Henriques of Tracerlab, Incorporated. Specifically, Dr. Henriques used Iodine 131 on human subjects in studying the behavior of Krim-Ko Gel. After study of the situation, the Subcommittee recommended that a strong letter be sent to Tracerlab, Incorporated. The letter should state that a recurrence of this type of violation will result in stopping shipments of radioactive materials to Tracerlab, Incorporated, and a thorough review of the entire situation by the highest authority in the Atomic Energy Commission. Such a letter was sent to Tracerlab, Inc. on April 11, 1949. Attached to these minutes are (1) a copy of letter dated April 11, 1949, from Paul C. Aebersold to William E. Barcour, Jr., (2) a copy of letter dated April 14, 1949, from William E. Barbour, Jr., to Paul C. Aebersold, and (3) a copy of memorandum dated April 14, 1949, from William E. Barbour, Jr., to selected members of the staff of Tracerlab, Inc.

V. Review of specific applications not yet acted upon by this Subcommittee.

No. 2431 - Southwestern Medical College - Allen F. Reid, J. B. Howell, P 32 in applicators for treatment of basal cell carcinoma. This application had been approved earlier on favorable

decision by three members of the Subcommittee, despite Dr. Friedell's objection. Dr. Friedell was concerned because of fear that P 32 might be too widely disseminated if used on filter paper plaques.

No. 2661 - Southwestern Medical College - Allen F. Reid, Gladys J. Fashena, for use in blood volume study in children. Dosage proposed is from one-fourth to one microcurie Phosphorus 32 per kilogram. This application was approved on February 14, 1949, after the Isotopes Division had received unqualified approvals from Dr. Hamilton, Dr. Holland and Dr. Quimby. No response had been received from Dr. Friedell. In response to a letter from S. A. Lough, dated January 26, 1949, to the members of the Subcommittee on Human Applications, Dr. Quimby sent the letter which is quoted, herewith:

> "In Dr. Failla's absence I am acting on the applications for isotope allotment.
>
> This morning your letter arrived concerning application 2661 for the use of P 32 in blood volume studies. I had approved this application and sent it back to you yesterday. The levels which they propose using, 1/4 to 1 microcurie of P 32 per kilogram of human host, are considerably below the levels calculated by Marinelli, Quimby and Hine, as that which will deliver .1 r in the first 24 hours. This is 2.4 microcuries per kilogram. If in children they keep to 1/4 microcuries per kilogram they have an extra factor of safety of 10.
>
> On this basis I still feel it reasonable to approve the application. They should, however, understand that repeats are not to be done on the same patient until after a considerable interval of time — several months — has elapsed."

On the basis of the three unqualified approvals and the statements in Dr. Quimby's letter, the allocation was made. Despite this previous action and the submitted opinions of three members of the Subcommittee, when Dr. Friedell opened the issue again,

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Dr. Holland and Dr. Failla thought that this application should be turned down. It was suggested that Dr. Reid should be asked to state the importance of making the study in children and that the dosage should be no larger than one-half microcurie per kilogram. Finally, the Subcommittee, assembled, decided that the Isotopes Division should make the allocation with the proviso that the Phosphorus 32 should not be used in children and with the statement that the Subcommittee on Human Applications will reconsider this decision if the significance of making the study in children is established. Since allocation has already been made, and in view of the careful analysis of the proposal which was made by Dr. Quimby, the Isotopes Division prefers to take no further action on this case at this time. When a request for a supplementary amount is received, the expressed desire of the Subcommittee will be applied to the situation.

No. 2778 - Ohio State University - Dr. Morton, Cobalt 60 needles. Request for 5000 plus pieces of Cobalt 60 wire is considered excessive. The allocation should not be made on a free basis because this is not interpreted as cancer research. The application is to be denied because so many pieces of active wire constitute too great a hazard. The Isotopes Division is to suggest to the applicant that he resubmit an application for a much smaller number of Cobalt 60 wires. This application and the decision of the Subcommittee are to be called to the attention of Dr. Aebersold. No communication is to be made to Dr. Morton until Dr. Hamilton's rating sheet has been returned.

The proposal of Tracerlab, Incorporated, to use Cobalt 60 in embalming fluids was disapproved on the basis that there was not adequate provision for long-term control of the radioactivity involved.

VI. Revision of Form AEC-313.

The Subcommittee urged that the application Form AEC-313 be revised so as to include spaces where the following information is specifically requested.

1. Dosage, both tracer and therapeutic.
2. The name of the compound administered.
3. Frequency of administration to the same patient.
4. The training and experience in the field of radioactivity possessed by the user.
5. An item to replace the one where the applicant is asked to check YES or NO regarding publication. The new item should read, "MAY WE RELEASE GENERAL INFORMATION REGARDING PROPOSED USE? IF NOT, PLEASE EXPLAIN."

VII. Development of method for replacement on some regular basis of members of the Subcommittee on Human Applications.

It was decided that a Subcommittee member would have a term of four years and that the terms would be staggered in such a way that one member would retire from the Committee each year. The Subcommittee members present drew lots to determine the order of retirement from the Committee. Dr. Holland drew the four-year term. Dr. Friedell drew the three-year term. Dr. Failla drew the two-year term. This left the one-year term for Dr. Hamilton. On the assumption that this drawing had been made one year ago

this permits Dr. Hamilton to retire at this time. It was felt that the appointment of a chairman of the Subcommittee on Human Applications should be left to the Atomic Energy Commission and that the Chairman should be reappointed each year. The Subcommittee suggested that Dr. D. Harold Copp be considered as a successor to Dr. Hamilton. The Subcommittee expressed its desire to recommend replacements on the Subcommittee's membership to the Atomic Energy Commission.

Proposed addition to this section (Section VII)

Dr. Hamilton has expressed his willingness to resign from membership on the Subcommittee on Human Applications to take effect as of July 1, 1949. The present membership of the Subcommittee recommends to the Atomic Energy Commission that this resignation be accepted. The Subcommittee recommends further that D. Harold Copp, M.D., Assistant Professor of Physiology, University of California Medical School, Berkeley, California, be appointed to succeed Dr. Hamilton for a term of four years from July 1, 1949, to July 1, 1953.

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ADDENDUM

Dr. Joseph G. Hamilton has proposed a slight modification of the rules governing approval of a request for a radioisotope to be used in human subjects.

On page 11 of the Tentative Minutes of Initial Meeting of the Committee on Isotope Distribution, U. S. Atomic Energy Commission, AEC Building, Washington, D. C., January 20, 1948, the following appeared under the caption "I. ACTION COMPLETED":

> "2. All requests for materials to be used in human subjects will be reviewed and rated by the four members of the Subcommittee on Human Applications. Allocation of materials based upon the recommendation of the Subcommittee will be made in the following manner:
>
> a. If a request receives four approvals, the Isotopes Division will promptly allocate the requested material.
>
> b. If the request receives three approvals, the Isotopes Division will allocate the requested material unless the fourth vote is a definite "NO". In the latter case the request will be resubmitted for rating to the Subcommittee along with the views of the dissenting member and a review by the Isotopes Division. If a request receives three approvals after the review, the Isotopes Division will allocate the material.
>
> c. If a request receives two approvals, the Isotopes Division will attempt to resolve the difficulties causing the two disapprovals and resubmit the request, along with a summary of the modified situation, for a second rating. No allocations will be made in such cases until approved by three members of the Subcommittee."

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the letter of June 21, 1949, from Dr. Hamilton to Dr. Aebersold, Hamilton wrote, as follows:

> "I am willing to accept the understanding that a request receiving 3 out of 4 votes for approval be allowed. However, whenever there is a dissenting vote, I wish to make the recommendation that the entire matter be reviewed again by the 4 members of the Subcommittee and a second poll be taken, the request being allowed even though one member still casts a negative vote.
>
> In the event of a 2 to 2 vote, the proposal should be reviewed a second time and if a 3 to 1 majority is not obtained, the request should be disapproved."

It is considered that these remarks by Dr. Hamilton are a reaffirmation of the Subcommittee's desire that the Isotopes Division follow the procedure outlined in the quoted minutes presented on page 16, immediately ending.

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Jo Topics

The Experimental Use of Radioactive Materials in Human Subjects at AEC Establishments.

DOE-C5104-A-26

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At the request of Dr. Shields Warren, Director, Division of Biology and Medicine, the Subcommittee on Human Application, Committee on Isotope Distribution respectfully submits the following recommendation:

1. Radioactive materials should be used in experiments involving human subjects when information obtained will have diagnostic value, therapeutic significance, or will contribute to knowledge on radiation protection.

2. Radioactive materials may be used in normal human subjects provided

a. The subject has full knowledge of the act and has given his consent to the procedure.

b. Animal studies have established the assimilation, distribution, selective localization and excretion of the radioisotope or derivative in question.

3. Radioactive materials may be used in patients suffering from diseased conditions of such a nature that there is no reasonable probability of the radioactivity employed producing manifest injury provided:

a. Animal studies have established the assimilation, distribution, selective localization and excretion of the radioisotope, or derivative, in question.

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b. The subject is of sound mind, has full knowledge of the act and has given his consent to the procedure.

c. Full description of experimental procedures and calculated estimates of radiation to be received by body structures and organs are submitted.

4. Investigations are approved (1) by medical director or his equivalent at the installation responsible for the investigation, (2) by the Director, Division of Biology and Medicine, and (3) full written descriptions of experimental procedures and calculated estimates of radiation to be received by body structure and organs must be submitted.

5. Radioisotopes and radiation doses are to be limited as follows:

1. Tissue radiation dose at the site of greatest concentration shall not initially be greater than 0.1 per day.

2. The effective net half-life which a combination of the biological and physical half-life of radioisotope and/or its derivative shall not be greater than 20 days.

3. Administered material limited to those emitting electrons and photons.

1019062

WAR DEPARTMENT
OFFICE OF THE SURGEON GENERAL
ARMY EPIDEMIOLOGICAL BOARD
UNITED STATES ARMY

~~OFFICE OF THE PRESIDENT~~
~~333 CEDAR STREET~~
~~NEW HAVEN, CONN.~~
Commission on Liver Disease
University of Minnesota Hospital
Minneapolis 14, Minnesota

April 5, 1948

Dr. Colin M. MacLeod
New York University
College of Medicine
477 First Avenue
New York 16, N. Y.

Dear Dr. MacLeod:

I have given careful consideration in the past few weeks to the matter of using volunteers in penal institutions for experimentation, with particular reference to hepatitis. Three weeks ago I had a conversation with Mr. Burnquist, the Attorney General of the State of Minnesota, with respect to the possibility of conducting experimental work on volunteers in the Minnesota penitentiaries. Mr. Burnquist was favorably inclined to the idea and quite optimistic about its feasibility. Later I had a lengthy discussion with Everett Fraser (Law School) Dean and with Mr. Vold of the Division of Criminology of the Department of Sociology in the University. I asked them specifically whether a waiver signed by the volunteers would be legal at a later date, insofar as avoidance of responsibility for disability or death was concerned. I asked this question both with respect to a waiver made out to the individual experimenter as well as to one assigned to the official agency sponsoring the research, that is to say, the Army Epidemiological Board of the War Department. They did not believe that such a waiver would be of much value, although they stated that so far as they knew there was no precedent in law to determine in advance what might happen in case of a suit. They pointed out that a clever attorney at some later date might very well be able to overthrow such a waiver and get a judgment against an experimentor in case of a disability or even succeed in having him declared guilty of homicide in case of a death.

Mr. Vold stated that there might be some recorded law touring on this whole matter in the state of Massachusetts. He points out that during the war volunteer prisoners were used for the testing "of synthetic blood serum", and that one or more deaths in addition to a number of severe illnesses resulted. He suggests one might get all the information about this from the Commissioner of Correction of the State of Massachusetts, State House, Boston. Mr. Vold also informed me of an interesting point that may have no bearing on the present matter; namely, that the brains of criminals executed in New York state are removed by law or at least

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FILE: Commission on Liver Diseases – Human Volunteers for Hepatitis Studies – Feb 1948 on

by state prerogative, but that the body is not available for dissection unless it is unclaimed. While this is probably not germane to the problem of using volunteers for experimentation, Mr. Vold thought that it might be of interest to determine whether there is any written law concerning this prerogative and, if so, how it has been established.

There is, of course, precedent for the use of volunteers for experimental purposes, as for example in Illinois and New Jersey. According to my legal friends, however, the responsibility for these experiments would devolve entirely upon the individual experimenter in case of a later suit or complaint. The mere fact that the warden or the state authorities give permission to the experimenter to ask for volunteers in no way removes his responsibility, nor does it place any of it on the state. This at least is the interpretation that Dean Fraser put upon the question, although he admitted that he knew of no law by which any real decision could be reached in advance.

I have given considerable thought to the matter of whether it would be advisable to approach individuals or groups in Congress with the idea of having laws passed relating either to payment of compensation for disability or release of the experimenter from liability. I am afraid that this would be a very dangerous course, and that it might infact, injure clinical investigations generally. There is a very real possibility that unfavorable publicity would quickly result. Dean Fraser and his colleagues were in thorough agreement on this point.

I have concluded then that any human experimentation must be carried out in the future as in the past, on the basis of the sole liability of the individual experimenter.

I should be glad to hear from you or from others to whom copies of this letter are being sent as to any alternative approaches to the problem that they may have in mind. I think it would be well if someone could look in the Massachusetts experience as mentioned above.

With kindest regards,

Sincerely yours,

C. J. Watson, M. D.

CW/vr

cc: Col. F. Bauer
Dr. W. P. Havens
Dr. J. Neefe
Dr. J. Stokes
Dr. J. Paul

P.S.: I do feel strongly, however, that if the Army approves and finances a specific research involving human experimentation, with the intention of accepting and utilizing any practical results therefrom, it should be willing to obligate itself to the protection of the experimenter, at least to the extent of purchasing a special insurance policy for each project of this type, covering disability or death. (By this I mean one comparable to a malpractice policy, protecting the experimenter against later suit for compensation. Obviously, no publicity should be given to this.)

DOOLEY HOSPITAL
MEDICAL COLLEGE HOSPITAL

MEDICAL COLLEGE OF VIRGINIA
HOSPITAL DIVISION
1200 EAST BROAD STREET
RICHMOND 19, VIRGINIA

April 8, 1948.

Dr. John Z. Bowers
Division of Biology and Medicine
Atomic Energy Commission
Oak Ridge, Tennessee

Dear Dr. Bowers:

We have recently obtained approval from the Isotopes Division for human use of P^{32} and have agreed to the condition that no more than 500 microcuries will be administered to any one patient within a period of six months. Several questions have come up which I would like some help in answering if you have the information

(1) Have you any advice as to the medical - legal aspects of experimental procedures in the human involving the use of radioactive isotopes when they are being used simply for investigational purposes and not for treatment of disease? I am speaking now of dosage levels, for example of P^{32}, 100-300 microcuries.

(2) Have any malpractice suits been instituted against individuals or institutions who have used radioactive material simply for investigation? Do you have any advice regarding insurance against such malpractice? If there have been suits, what has been the court ruling in such instances?

(3) Does your isotope group think it advisable to have the patient sign permission forms for the experimental use so that later medical-legal action is obviated?

I realize I am asking for information in realms where practices are not standard or well established but will appreciate very much any aid you can give us so that our position here is clear and sound.

Very truly yours,

Everett Idris Evans

Everett Idris Evans, M.D.
Professor of Surgery.

cc: R. Woodruff.
EIE:rt

DISPOSITION FORM

FILE No.	SUBJECT
[illegible]	Human Volunteers for Research Investigations

TO	FROM	DATE	COMMENT No. 1
Chief, Legal Office SGO Room 2B520	Ass't Administrator Army Epidemiological Board Room 2B460	23 April 1946 Major George F. Rumer, MC	sm/72647

1. It is requested that this office be furnished more specific information on the subject of human volunteers in research experiments carried out by the Army. More specifically, it is desired that the Legal Office take such action as may be necessary to adequately answer the following in particular:

a. Would a waiver releasing an experimenter from any further liability insofar as the volunteer is concerned be of value in case of a suit of death or disability at a later date? (See ltr from Watson dated 12 April)

b. Is there a specific recorded law on this subject in the State of Massachusetts? It is suggested that information be obtained from the Commissioner of Correction, State of Massachusetts, State House, Boston, Massachusetts. (See ltr from Watson dated 5 April)

c. Can the Army obligate itself to the protection of its responsible investigators, at least to the extent of purchasing a special insurance policy for each project of this type, covering disability or death? (See ltr from Watson dated 5 April)

2. Any additional information and advice on this subject is desired by this Board, particularly as related to Army policy and legal regulations. It is further desired that this matter be expedited so that it may be discussed at the annual meeting of the Army Epidemiological Board on 6 May 1946.

3. The complete files of this office on this subject are attached hereto for ready reference. It is requested that they be returned when they have served their purpose.

GEORGE F. RUMER
Major, Medical Corps
Assistant Administrator
Army Epidemiological Board

Inclosure
Corresp.
(see par. 3)

DA AGO FORM 1 OCT 47 897 Replaces WD AGO Form 897, 1 May 46, which may be used.

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RECORD GROUP: 334
ENTRY: 14
FILE: Commission on Liver Diseases - Human Volunteers for Hepatitis Studies - Feb 1946 on

JZBowers:lmr

2

April 27, 1948

Everett Idris Evans
Professor of Surgery
Medical College of Virginia
1200 East Broad Street
Richmond 19, Virginia

Dear Dr. Evans:

Thank you for your recent letter requesting information regarding isotopes. In view of the fact that this information is more readily available from the Isotope Division at Oak Ridge, I am taking the liberty of forwarding a copy of your letter to Dr. Paul Aebersold and requesting that he reply to it directly to you.

I hope that you finally got together with Dr. Mitchell for he remembers pleasantly having met you in England.

I will always be glad to help you with any problems that may arise in the field of atomic energy.

Yours sincerely,

John Z. Bowers, M. D.
Ass't. to Director
Division of Biology
and Medicine

In Reply Refer To:
AGC:OSH

Oak Ridge, Tennessee
May 14, 1948

ATOMIC ENERGY COMMISSION
File No. AEC 441.2 (R-Virginia, Medical College of)

Dr. Everett I. Evans
Professor of Surgery
Medical College of Virginia
1200 E. Broad Street
Richmond 19, Virginia

Dear Dr. Evans:

Your letter of April 8 to Dr. Bowers has been referred to me for answer.

The questions posed in your letter are certainly important ones, and I recognize the serious disadvantages in proceeding with investigations without knowing your legal position. I regret to say, however, that we can be of but very little assistance. You appreciate the fact, I am sure, that the answers to these questions would involve legal opinions on matters concerning the activities of the College and its relationships with other private parties. Under these circumstances we feel that it would not be appropriate for us to furnish legal advice to either party of a private business relationship. About all I can say is that we have not heard of any malpractice suits being instituted in connection with the use of radioisotopes for investigational purposes. Also, we understand that most hospitals do require patients to sign general releases before entering for treatment.

If we can be of assistance in regard to problems concerning your investigations, please feel free to write as we are interested in helping when we can.

Very truly yours,

Nathan H. Woodruff
Chief, Technical Branch,
Isotopes Division

cc: Dr. John Z. Bowers,
Washington, D. C.

Hiestand:rm

	Legal	P.G.C.	Isotopes			
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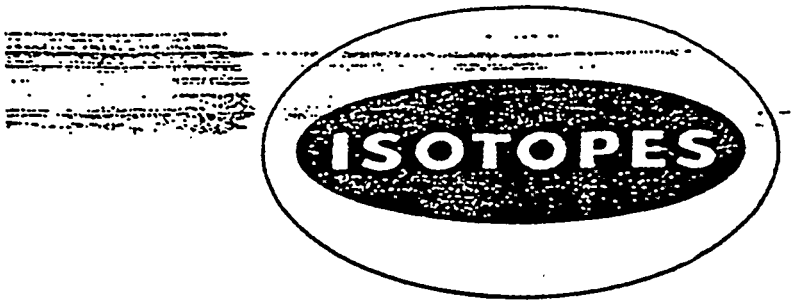

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September 1949

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July 1949

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Box 1

CONTENTS

ISOTOPES DIVISION
U. S. ATOMIC ENERGY COMMISSION
OAK RIDGE, TENNESSEE

AEC, Oak Ridge, Tenn.-9-22-49--5,000-A13284

DISTRIBUTION OF ISOTOPES FOR CANCER RESEARCH

Reference: Isotopes Division Catalogue and Price List No. 3, July 1949, page 7, "Radioisotopes Free of Production Costs for Cancer Research."

Cancer research is interpreted to include the following:

1. Investigation of the basic aspects of normal and abnormal cellular growth.
2. The development and evaluation of therapeutic and diagnostic procedures for cancer and allied diseases.

Considerable interest has been expressed concerning the use of Cobalt 60 as a radiation source in the treatment of cancer. The use of Cobalt 60 needles is not considered research by the Subcommittee on Human Applications unless the needles are of some unusual design, or incorporate some unusual feature. Similarly, if multicurie sources of Cobalt 60 are considered as substitutes for other high energy gamma or X-ray sources for teletherapy units, the proposed use would be looked upon as cancer research only if the techniques to be employed departed from those already established for the gamma or X-ray sources, or if a considerable program is to be undertaken with the unit on the biological effects of radiation.

THE USE OF RADIOISOTOPES IN TRACER STUDIES IN HUMAN SUBJECTS

Reference: Isotopes Division Catalogue and Price List No. 3, July 1949, page 30, "Allocation Policy for Radioisotopes for Use in Medicine.

I. NORMAL ADULTS

A. Beta and Gamma Emitters with a Biological Half-Life of 20 Days or Less.

Applicants who desire to use radioisotopes in normal adults should submit a statement of the results of animal experiments, or adequate reference to the literature, concerning the following points:

1. Metabolism and distribution of the radiomaterial in the form administered.
2. The tissue of highest concentration and the relative concentration therein.
3. The relative concentrations in the tissue of interest and particularly radiosensitive tissues such as the gonads and hematopoietic system.
4. The biological half-life of the radioisotope in the tissue of highest concentration, the tissue of interest and the particularly radiosensitive tissues.

B. Beta and Gamma Emitters with a Biological Half-Life Greater than 20 Days.

In general, for isotopes with a biological half-life greater than 20 days, the dosage in the critical tissues should be such as to conform to the limitations which will be set by the National Committee on Radiation Protection. In special cases, however, the Subcommittee on Human Applications may permit the use of such radioisotopes in higher dosages.

In view of recently accumulated information, the Subcommittee on Human Applications is prepared to consider applications for use of certain Carbon

[illegible] compounds in human subjects.

Each request for "long-lived" radioisotopes to be used in humans will be reviewed separately by the Subcommittee on Human Applications.

II. NORMAL CHILDREN

In general the use of radioisotopes in normal children is discouraged. However, the Subcommittee on Human Applications will consider proposals for such use in important researches, provided the problem cannot be studied properly by other methods and provided the radiation dosage level in any tissue is low enough to be considered harmless. It should be noted that in general the amount of radioactive material per kilogram of body weight must be smaller in children than that required for similar studies in the adult.

III. NORMAL PREGNANCY

The Subcommittee on Human Applications feels that the use of radioactive materials in all normal pregnancies should be strongly discouraged where no therapeutic benefit is to be derived.

IV. SPECIAL PATHOLOGICAL CONDITIONS

It is recognized that there may be instances in which the disease from which a patient is suffering permits the administration, for investigative purposes, of doses larger than those recommended above for use in normal subjects. Applications for such uses of radioisotopes will be given special consideration by the Subcommittee on Human Applications, providing:

1. Full responsibility for conduct of the work is assumed by a special committee of at least three competent physicians in

the institution in which the work is to be done. This will not necessarily be the local Radioisotope Committee.

2. The subject has given his consent to the procedure.

3. There is no reasonable likelihood of producing manifest injury by the radioisotope to be employed.

FIELD AND INDUSTRIAL USES OF LONG-LIVED RADIOISOTOPES

The primary problem involved in field and industrial uses of radioisotopes is that of safety control and accountability. If a radioisotope is to be used under other than laboratory conditions, the plan should provide for long-term control of the activity. The amount of activity involved is an important consideration. So also is the type of radiation emitted by the radioisotope in question. The likelihood of exposure to radiation of persons who could have no knowledge of the presence of the radioactive material, or of its potential danger, must always be considered.

FIELD USES

An application for use of a radioisotope in a field study should usually be supported by:

1. A detailed outline of the experiment.
2. A map of the area, showing topography.
3. A full description of the distribution of the human population and the livestock population in and near the experimental areas.
4. A statement concerning the relationship of the experimental area to water-sheds from which domestic water supplies are collected.
5. A description of the underground strata with reference to likelihood of movement of water and fixation of activity by mineral components.
6. A statement regarding the degree of control which can and will be maintained over the experimental area.

INDUSTRIAL USES

Industrial applications of radioisotopes fall into three general groups:

1. Cases in which the activity is mounted in a device used to control industrial processes.
2. Cases in which the activity is used in a process, but does not appear in any product sold to the public.
3. Cases in which the activity would be present in products sold to the public.

In the first situation the factors to be considered are much the same as are pertinent to use of radioisotopes in laboratories. If the activity is well shielded, otherwise controlled, and under the supervision of trained workers, the use would be considered feasible.

The third case raises the question as to the level of activity which might be permitted in products sold to the public. The situation is somewhat different for beta emitters than for gamma emitters.

a. Beta ray emitters.

Proposals to incorporate beta emitting radioisotopes in products offered for sale can be approved if (1) the radioactive substance is in insoluble form and incorporated permanently in inert material, and (2) the product produces no more radiation than 0.3 rep per week at the surface.

b. Gamma ray emitters.

Products containing gamma emitters must meet the conditions outlined above for beta emitters. In addition, when products are stored in warehouses, monitoring must be done to show that the radiation level

is in accord with the limits stated in the handbook "Safe Handling of Radioisotopes," issued by the National Committee on Radiation Protection.

STANDARD FORM NO. 64

Office Memorandum · UNITED STATES GOVERNMENT

TO: A. H. Holland, Jr., Director of Research and Medicine
DATE: October 5, 1949

FROM: Paul C. Aebersold, Chief, Isotopes Division

SUBJECT: USE OF RADIOISOTOPES IN HUMAN SUBJECTS

IR:SAL

Reference is made to communication of August 11, 1949, sent to you by Dr. Shields Warren, Director, Division of Biology and Medicine, regarding allocation of radioisotopes to be used in human subjects. It is noted that Dr. Warren instructed that such allocations would be made by the Isotopes Division only after review and approval by the Subcommittee on Human Applications of the Committee on Isotope Distribution. It should be emphasized that the instruction applies even though the radiomaterial is produced in the laboratory where it is to be used.

Since this procedure has not been uniformly followed in the past, we are writing to acquaint you with the appropriate details. Enclosed is a copy of our latest catalog. On pages 30 and 31 are presented the criteria governing the distribution of radioisotopes when these substances are to be used in humans. Enclosed also are six copies of Isotopes Division Circular D-4, which contains the same statement, and which may prove convenient to you in the process of acquainting members of your staff with this procedure.

Obviously applicants for radioisotopes to be used in human subjects will need to submit more information than has been offered on previous applications submitted on Form AEC-558. For the convenience of this office and of the Subcommittee on Human Applications, applications should be submitted on Form AEC-313. Special attention should be given to the information asked for on pages 30 and 31 of the Catalog and Price List No 3, July 1949. We shall assume, as in the past, that instrumentation, both for measurement and for health physics purposes, is adequate at Commission laboratories. It will not be necessary to use Part 2 of Form AEC-313. The Subcommittee has insisted that a physician be connected with all projects in which human subjects are used, so as to insure that the clinical care of the patients will be provided for. It should be emphasized that each application should be accompanied by a formal, written endorsement, signed by the Chairman of the local "Isotopes Committee," the recommended membership of which is outlined on pages 30 and 31 of the catalog. Your special attention is called to the Subcommittee's insistence that a complete dosage schedule be submitted with the application.

OCT 7 - 1949
ISOTOPES PROGRAM

No. _____

OAK RIDGE INSTITUTE OF NUCLEAR STUDIES

Oak Ridge, Tennessee

APPLICATION FOR ADMISSION TO THE

MEDICAL DIVISION HOSPITAL

The Oak Ridge Institute of Nuclear Studies, Medical Division, has a 30-bed hospital unit as a part of its research facilities in Oak Ridge. The purpose of the hospital is to seek and develop new methods of diagnosis and treatment and to study fundamental problems of certain diseases in the hope that the information obtained can be used for the practical treatment of these diseases and the benefit of patients. The hospital, which is staffed by qualified physicians and nurses, is especially designed for the use of radioactive isotopes. Because of the nature of the facilities, only certain types of diseases can be studied and treated.

The applicant recognizes the right of the hospital to determine the eligibility of all persons for admission as well as the right to refuse admission to any applicant. Moreover, the hospital reserves the right to discharge the patient at such time as it deems advisable.

No charge is made for hospitalization and treatment in the research hospital. The hospital endeavors to provide the most complete care for the patient and the patient's welfare is the primary concern of the hospital. However, the applicant must understand and appreciate the fact that some of the treatments that will be used are new, are based upon experiments on animals and that the degree of probable benefit, if any, cannot always be predicted in advance. The applicant is expected to fully cooperate at all times with the hospital and its staff. The applicant hereby grants permission for such operations, and biopsies as are deemed necessary and advisable by the hospital. It is agreed that the hospital may take photographs of the applicant and his or her treatments, procedures, operations, etc., which are performed upon the patient while in the hospital and use the same in scientific publications. At the time of admission to the hospital the applicant will be required to sign such further agreements as may be required by the Institute and at all times comply with the rules and regulations of the hospital.

On the basis of the foregoing, admission to said hospital is requested by _____

This _____ day of _____, 19__.

Applicant _____

_____

Father or Guardian

_____

Mother

This application should be submitted to the nearest participating medical school listed in the patient information pamphlet. It should not be sent directly to Oak Ridge.

APPROVED BY:

_____

_____

Title

for _____ Medical School

ACCEPTED BY

_____

_____

Title

OAK RIDGE INSTITUTE OF NUCLEAR STUDIES

WAIVER AND RELEASE

In consideration of my being selected, accepted and admitted as a patient in the research hospital conducted and operated by the Oak Ridge Institute of Nuclear Studies, a nonprofit corporation, at Oak Ridge, Tennessee, for hospitalization and the receiving of medical treatment, attention and care by experimental methods and means and/or otherwise, I, _____, for myself, my heirs, executors, administrators and assigns, do hereby release, acquit and forever discharge said Oak Ridge Institute of Nuclear Studies, its officers, physicians, nurses, agents, servants and employees, their heirs, successors and assigns, and each of them, of and from any and all actions, causes of action, claims, demands, damages, loss, costs and expenses, whether direct or consequential, arising or claimed to arise because of or as the result of my said hospitalization in said hospital and/or any treatment and care while a patient in said hospital or by reason of my having been a patient therein.

I acknowledge that I have been fully advised by the Oak Ridge Institute of Nuclear Studies concerning the character and kind of treatment and care which I will receive as such patient and I understand that for the most part, they will be experimental with no definite promise of improvement in my physical condition. Notwithstanding such fact, I have executed this agreement for the purposes herein contained of my own free will and choice. I covenant that I have not been influenced to any extent whatever in making this release by any representations or statements regarding my physical condition or the possible results of any treatment therefor, and I hereby expressly assume all risks thereof.

I further understand that but for this agreement on my part, I would not be accepted by the Oak Ridge Institute of Nuclear Studies as a patient in its said hospital.

I covenant that I have carefully read the foregoing and know the contents thereof.

IN WITNESS WHEREOF, I have hereunto set my hand on the _____ day of _____, 19__.

_____
Applicant

ATTEST:

_____
Father or Guardian

_____

_____
Mother

_____

STATE OF TENNESSEE

COUNTY OF ANDERSON

Personally appeared before me, _____, a Notary Public in and for the State and County aforesaid, the within named bargainer, _____, with whom I am personally acquainted, and who acknowledged that he executed the foregoing instrument for the purposes therein contained.

WITNESS my hand and official seal in _____ County, Tennessee, this the _____ day of _____, 19__.

_____
Notary Public

My commission expires: My com. expires June 10, 1961.

AEC, Oak Ridge, Tenn. 9-15-1000-A7773

husband of , do hereby join in the execution of the foregoing waiver and release for the purpose of releasing Oak Ridge Institute of Nuclear Studies and all others named above from any and all claims, actions, and demands of every character whatsoever growing out of or in any wise incident to the contemplated hospitalization and treatment of said wife,

Signed: _____

Witnessed:

_____

_____

Date _____

IRRADIATION OF HUMAN SUBJECTS AS A MEDICAL EXPERIMENT

Robert S. Stone, M. D.
Professor of Radiology, University of California School of Medicine
San Francisco

THE NEED

If the Air Force, with the help of Nepa, succeeds in getting a nuclear powered aircraft, it is very unlikely that it will be possible to shield the crew in such a way that they will not receive larger than maximum permissible exposure to radiation on any one mission. If another war develops and the Army is called upon to occupy territory that has previously been bombed by a nuclear powered weapon, the troops will have to be exposed to greater than usually permissible amounts of radiation; and the same can be said for the Navy if the men because of necessity have to operate a ship that has been contaminated. In all of these instances both those who have to direct the forces and the men themselves will want to know what the risks are at various levels of radiation exposure. It is extremely important that those in command can talk intelligently and convincingly from experience gained on human beings.

During and since the last war, millions of dollars have been spent by the O.S.R.D., the Manhattan Project and the Atomic Energy Commission to carry out experiments with animals aimed at determining the effects of levels of irradiation, using single, multiple and chronic exposures. In general, the conclusion has been reached that, not only each species of animal differs from every other in their responses, but also various strains within a specie differ. The differences can be found both when studying lethal effects of large doses and minimal effects of small doses. Moreover, it has not been possible to get agreement as to how

extrapolate from the results obtained on animals to the results to be expected on humans. The Radiologists, through a committee appointed by the Radiological Society of North America, tried to reach some conclusions from their clinical experiences with patients as to what changes might be expected from various levels of radiation. The answers given by the various doctors to questions asking for the amounts of radiation required to produce specific effects were so divergent that one cannot use them with any feeling of confidence. While some physicians are willing to make very positive and definite statements, others with equal experience in therapeutic radiology are willing to contradict the first group. All of which means that from previous experience no uniform conclusions can be drawn.

When anyone attempts to tell people that it is perfectly safe to do a particularly hazardous job, using as the basis of their statement animal experiments, it does not have nearly as convincing an effect as the statement that previously human beings have gone through similar experiences without deleterious effects.

THE HAZARDS

When one speaks of doing experiments with radiation exposures using people, it is necessary to consider what type of exposures are contemplated. With the use of animals it is frequently customary to start experiments with exposures that will cause the death of the animal and from that figure work down to the dose that will cause the minimum detectible changes. The procedure could not be contemplated in the case of human experiments. Having learned from animals the qualitative effects that are to be looked for, one can start with minimum doses which will be expected to cause no detectible

effect and work from these to higher levels where minimum effects might be detected.

It must be admitted that any amount of irradiation causes some genetic effects, but within the ranges that should be utilized from human experimentation the number of increased genetic changes would be so small as to be undetectible.

One effect of irradiation which could be detected when no other effects were discernible was the shortening of the life span. However, this can be detected at low levels only by statistics covering whole groups, not in a particular individual case. It would therefore be somewhat theoretical in the ranges that should be utilized in human experiments. Changes in the peripheral blood would probably be the first changes to be noted within the low ranges of exposures of humans, but at the low levels of exposure would be slight and transcient.

Members of the Nepa Medical Advisory Committee drawing on their own and their fellow scientists' experiences, felt that with doses below 150 r there would be so small a chance of producing any <u>late</u> effects that such effects as the production of leukemia could be entirely ruled out.

A plan of attack could be to first expose some people to 25 roentgens of total body irradiation and observe them for a period of time. Such a level of exposure is not too uncommon in the practice of radiology. It has been used in the treatment of patients with arthritis, generalized cancer, polycythemia vera and leukemia. If and when it is found that a significant number of relatively normal people exposed to 25 roentgens have shown no significant changes than the experimentors could to to double this dose, namely, 50 roentgens. The next logical step would be to give 50 roentgens and repeat it in a week; if nothing happened at this level they could then proceed to expose normal people to 100 roentgens and probably to 150 roentgens. Exposure of

order and magnitude are not new and have been given to human beings who were sick. From this experience with sick people it seems unlikely that any particular person would realize that any damage had been done to him by such exposure.

To be able to tell a group of pilots that normal human beings had been voluntarily exposed without untoward effects to larger doses than they would receive while carrying out a particular mission, would be of inestimable value. The extremely small hazard of undetectible genetic effect, undetectible effect on the life span and possibly slight effect on the blood picture are the extremely small hazards that must be weighed against the value of having actual experience with exposure of humans.

PRECEDENTS

The use of human beings in medical experiments is not new and the hazards involved in any particular experiments have often been much greater than those contemplated here. In fact one might say that the mass voluntary experiment which the American public is now carrying out with the antihistaminics is fraught with more uncertainty than would be these proposed experiments with radiation. No one has as carefully studied animals taking antihistaminics over a long period of time as they have studied animals receiving radiation. Without going into ancient history one might point out that in 1798 Jenner used human beings to experiment with his vaccination against smallpox. The experiments of Walter Reed with the yellow fever is another evidence of the uses of human beings for medical experiments even when the possible result was death. During the recent war, prisoners in federal and state prisons were used in several different types of medical experiments, notably those involving the testing of drugs for the treatment of malaria and those involving the use of

~~malaria~~ substitutes. The United States Public Health Service was involved in experiments conducted on prisoners inthe federal correctional institution at Seageville, Texas. The Illinois state prison at Statesville was used for malaria work in which the armed forces were involved. In medical schools students frequently volunteer to try the effects of drugs on themselves.

It is thus obvious that the use of volunteers, whether obtained from among prisoners, scientific circles or army groups, is not unusual.

THE ETHICS OF HUMAN EXPERIMENTATION

Doctor Ivy opened his discussion of "The History and Ethics of the Use of Human Subjects in Medical Experiments" with the following paragraph: "Ethics means thinking sincerely about rules for human conduct. Experimentation is a highly intellectual form of human activity. Hence, it is appropriate for experimentors to consider the ethics of their activities." (Science, July 2, 1948, Vol. 108, page 1.) He goes on to show that the most important requirement in the ethical use of human beings as subjects in medical experiments is that they be <u>volunteers</u> and further he states that voluntaering exists when a person is able to say yes or no without fear of being punished or of being deprived of priveleges due him in the ordinary course of events, and I might add, without the "undue pressure" of a promise of some great reward other than self satisfaction.

The House of Delegates of the American Medical Association laid down three requirements to be satisfied in connection with ethics. First, the voluntary consent of the person on whom the experiment is to be performed; second, the danger of each experiment must previously be investigated by animal experimentation and third, the experiment must be performed under proper medical protection and management. A Committee appointed by Governor Dwight H. Green of Illinois, to consider the ethics governing the service of prisoners as subjects in medical experiments after pointing out that medical scientists, medical students, soldiers, sailors and other volunteers have on

many occasions served as subjects in medical experiments designed to advance human welfare, enlarged on these ethical statements in the following way:

"1. Consent of the human subject must be obtained. All subjects have been volunteers in the absence of coercion in any form. Before volunteering, the subjects have been informed of the hazards, if any."

"2. The experiment to be performed must be based on the results of animal experimentation and on a knowledge of the natural history of the disease under study and must be so designed that the anticipated results will justify the performance of the experiment. The experiment must be such as to yield results unprocurable by other methods of study which are necessary for the good of society."

"3. The experiment must be conducted (a) only by scientifically qualified persons and (b) so as to avoid all unnecessary physical and mental suffering and injury and (c) only after the results of adequate animal experimentation have eliminated any a priori reason to believe that death or disabling injury will occur. If there is any a priori reason that accidental death or disabling injury may occur, as in such experiments as those of Walter Reed in which the mosquito was demonstrated to transmit yellow fever, then medical scientists should serve or should have served as volunteers along with nonscientific personnel." (Journal of the American Medical Association, February 14, 1948, Vol. 136, #7, page 457.).

In the proposed experiments:

a) The subjects can be volunteers and can be told of the hazards.

b) The human experiments can be based on animal experiments.

c) The anticipated results will justify the performance of the experiments.

d) The results cannot be procured by any other method of study.

e) The results are for the good of society as a whole.

f) There is no a priori reason from animal experiments and human experi-

to expect unnecessary physical or mental suffering.

PRECAUTIONS

When the experiments are done they must be conducted by scientifically qualified persons.

Adequate animal experiments and medical use of radiations on sick people have already eliminated any possibility that death or disabling injury will occur as a result of the proposed experiments. The use of patients (sick people) has not given all of the answers desired because they were abnormal to begin with and often respond abnormally.

MAY USE PRISONERS

If one were to be satisfied with the results from radiation exposure that might occur within the first few weeks or months, any group of volunteers would be useful, but since one wants to know what will occur years after an exposure it will be necessary to have a group such that all of them can be followed for a long time. Life prisoners are the one group of people that are likely to remain in one place where they can be observed for a great many years.

LOCATION OF EXPERIMENTAL APPARATUS

To carry out experiments of the type envisaged will require that the conditions of exposure be as nearly similar to those of members of the armed forces as possible. To meet this condition requires that the body as a whole be exposed rather than any part and that the exposure be with a penetrating type of radiation. Of course the best source of radiation would be an atomic pile shielded in one area by the same materials as might be used in an aircraft. This would be an extremely difficult procedure and would tie up a nuclear power plant for a considerable amount of time. The conditions could be moderately simulated by using penetrating x-rays from a 250 or more kilovolt x-ray machine or by using the gamma rays from a radiocobalt bomb. In either event the source of the radiation would have to be a t a considerable distance from

volunteers. This requires a relatively strong source, a relatively large room and adequate protection around the room. This would be a rather expensive installation and therefore could not be moved around the country to different locations. A large prison with a large relatively fixed population would seem to be the ideal place to establish such an installation.

In addition to the requirement for irradiation, it will be necessary to have good clinical facilities and laboratories to carry out a number of tests by a relatively stable group of investigators.

The constancy of the population, the ability to have continuity of observation, and the economic use of equipment — all point to the conclusion that a prison provides the best location.

OTHER CONSIDERATIONS

It should be borne in mind that for the purpose of obtaining short term results, other types of volunteers than prisoners might be used and valuable information obtained. Patients with incurable cancer such as those having multiple metastases might volunteer. In order that the results from experiments using them could be of any value, only those should be used who could be expected to be free from constitutional symptoms from their cancer for several months following their treatments.

Certain scientists might be willing to volunteer for specific doses, but here again the likelihood of their being followed with any consistency of observation over long periods of time is slight. They move around the country so that the same clinical and laboratory groups could not follow them.

There are numerous people in the general population who might volunteer their services, but here again the possibility of consistent controlled observation is the big handicap.

The use of individuals below 21 years of age should not be permitted

under any conditions because such individual cannot legally volunteer. However, those below the menopause (unless they have incurable cancer) probably should not be used because of psychological factors.

CONCLUSIONS

Most people fear known hazards to life, but when they can calculate or think they can calculate the risk and when they understand or think they understand the hazard, they are often willing to go ahead. On the other hand, when the risk is not calculable and the danger is not understood, people are more likely to be mentally disturbed at exposing themselves to such conditions. While a great deal is known now about radiation hazards insofar as animals are concerned, we know relatively little so far as the normal healthy human being is concerned. We know that radiations can kill people from the experiences at Los Alamos, Nagasaki and Hiroshima; but we do not know the dose required to kill. We know that doctors who have received daily exposures under the normal amounts have developed cancer of the skin or leukemia, but we do not know the doses that they received. With the increasing use of x-rays for diagnostic purposes and of radioactive materials for investigative diagnostic and therapeutic purposes, we are likely to learn more in the future about single and repeated exposures to radiation, but the data will be inaccurate.

The value of one or two good controlled experiments on a limited population over a period years would be of inestimable value to the advancement of knowledge of radiation effects. The ability to say to armed troops and civilian communities that you know from experiments on humans what the effects of the radiations will be both in regards to short termand long term effects, and thus to place their knowledge of radiation dangers inthe same category as the knowledge of the hazard of flying over enemy territory, would be of inestimable value.

SO 4 5 6

FAIRCHILD ENGINE AND AIRPLANE CORPORATION
NEPA DIVISION, P. O. BOX 415, OAK RIDGE, TENN.

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L5-2/M3-4

MEMORANDUM FOR THE SECRETARY OF DEFENSE 24 Apr 1950

Subj: Recommendation that the Armed Services conduct experiments on human subjects to determine effects of radiation exposure

Ref: (a) Memorandum to Secretary of the Navy from Director of Medical Services of 3 April 1950

1. The Panel on Atomic Warfare of the Research and Development Board has agreed that accurate experimental data on the biological effects of known levels of radiation exposure in human subjects is essential for complete knowledge of the problems involved.

2. It is believed that the procedures proposed by the Chairman of the Subcommittee of the NRPA Medical Advisory Committee are sound from a research point of view. It is further believed that the proposal to use long-term prisoners, with the safeguards of exposure levels and the insurance of a true volunteer status, meets the requirements of accepted American standards for the use of human subjects for research purposes.

[illegible]
Under Secretary of the Navy

Prepared by: Rear Admiral F. C. Greaves (MC) USN
Assistant Chief of Bureau for Research & Medical
Military Specialties, BuMed
Potomac Annex, Bldg. 4, Rm. 34
Ext. 5110
18 Apr 1950

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FILE M & S CORRES. FILES

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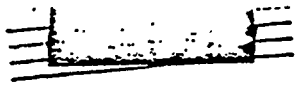
ADMIRAL GREAVES: Well, Dr. Dunham has given a very excellent description of the experimental work and studies that are being carried on in many fields. Our problem in the Navy is of course similar to that of everyone else. Our personnel will be liable to injury and liable to become casualties the same as anyone else, so we are interested in all those explorations in the field of hemmorrhage and infection and the other things in prevention. In addition to that we do have some problems that are peculiar to the Naval service.

For example, being a sea-going outfit, we are particularly interested in material damage to the vessels and to contamination that might follow the type of explosion that would occur under conditions at sea. This subject has been studied and is being studied out at the research laboratories at Hunter Point, and they have discovered some interesting things.

For example, they have found that contamination is reduced very markedly if the surfaces are wet at the time the contamination occurs. If the contamination occurs on a wet surface the decontamination can be effected to an extent of about 98 percent. If the contamination occurs at a time while the surfaces are being wet, they are being flooded with sea water for example, it can be reduced to 99 per cent.

If they can work out some system of getting an alarm to start flooding the weather decks of the ship and then cut off the flooding so that they won't be flooding contaminated water from over the side, and get out of that area where there is an amount of good pure water, they [redacted] net aproblem which is very important.



Another thing that we are interested in is something that has not been mentioned here, or I missed it if it was, and that is the effects upon personnel in a submarine, for example, if we succeed in powering such a submarine with an atomic engine.

We know that personnel that are subjected to radiation, doses of radiation, if they are put at rest, their chances for recovery are pretty good in many cases, but that condition does not prevail in a submarine. They must keep on the job, and there is an element of work and fatigue and all of that sort of thing which we all know increases the effect of radiation.

That is aproblem that is more and more coming to be thought of by our prople that are interested in this.

Of course, we are also interested in a way if it is possible, to protect individuals against the effects of radiation prior to their being exposed to radiation. Dr. Kruger out in Berkeley and the people across the Bay at Hunter's Point are working on experiments and projects on that line.

I have brought with me two people who know more about our radiation problems and perhaps they might have something to say.

CAPTAIN BEHRENS: I have nothing much more to add. We are naturally interested in the contamination and decontamination because of the increased susceptibility to the effects of an under-water burst and as Admiral Greaves pointed out that problem is of considerable concern, and also the problems that might be associated with nuclear reactors. That brings in the whole matter of calculated risk which all of the services are interested in, and it is not only the services but probably the civilians as well.

There is no way of telling, in certain localities, at any rate, whether or not there might not be an under-water burst. In most places it is quite obvious that such a use of an atomic bomb would not be profitable, but here and there it might be, and of course there might be a ground level burst.

The net outcome of that would be that you might be faced with the necessity of sending rescue parties or salvage parties into contaminated areas either for purposes of rescue or again for purposes of following up in the military venture. So the problem of calculated risk comes in, and that is of course an area in which we would like more information. We have plenty of information about patients but we don't have too much information as to what the effectiveness of personnel are going to be if they are exposed to something like in the neighborhood of 100 R, because it is a different proposition when they are working than if they are patients, and can lie down and rest and get good medical attention between the times when they get the treatment.

They are interested in seeing how effective they will be and how much their morale might suffer and how the remote effects might be affected by the amount of work and effort and exposure to various aspects of the environment. That orginarily doesn't cause us too much concern, that is exposure to heat and exposure to cold and fatigue.

We usually don't think too much of that, but when it is added to radiation, it could make quite a difference. For instance, we have lost several sets of experimental animals in which they were studying the LD-50 because the truck broke down and they were exposed to hot weather for a few hours and then the whole outfit died instead of as some reduced percentage of them. [redacted]

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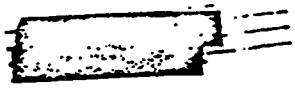


So that is the type of problem I think we are all interested in, both civilian and military. That is about all that I have to add to the discussion.

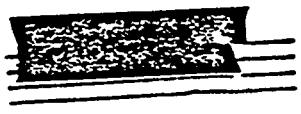
CAPTAIN HAIGHT: I think the only thing that I could add that might have some value would be a question of anoxia. It has already been proved definitely that extreme anoxia has a protective effect, and the aviators are particularly interested in that. They would like to run that from extreme anoxia to partial anoxia, and see if partial anoxia would give some protective effect because the condition of the atmosphere in a closed cabin plan can be quite carefully controlled. It would be theoretically possible if a modern anoxia was helpful to produce that effect within the plane.

DR. WARREN: Have you in mind the figures of Dr. Dowdy's experiments, Dr. Dunham?

DR. DUNHAM: His was something like 90 per cent or 95 percent nitrogen and 5 per cent carbondioxide, and it was practically total anoxia, and the Argonne National Laboratory has followed on with some smaller organisms in the same type of work, and I don't believe they have found appreciable effects unless they go back practically to the whole limit.

I wouldn't perhaps want to go on record with that statement, but I think that is what they have pretty well decided. It has got to be a really gross anoxia.

DR. WARREN: I would like to ask General Powell what he would regard as the pretty critical level as far as oxygen is concerned, and where would he start to worry about the ability of the pilots to properly carry out their job or the bombardiers to do their work performing it properly.



GENERAL POWELL: Well, 10,000 feet is the general level at which we require them to take oxygen because of the effect on night vision.

DR. WARREN: So that any significant amount of anoxia as a means of radiation protection at least, you would be afraid of that from the operational standpoint?

GENERALPOWELL: That is right.

CAPTAIN HAIGHT: I have nothing further. Thank you.

GENERAL COONEY: General Bliss was unable to attend this afternoon and he send his regrets. I didn't know until fifteen minutes ago that I was to substitute for him.

The Army is doing very little work on ionizing radiation because they feel that the field has been so well covered. They are very much interested in the thermal burn problem and they are carrying on extensive studies along this line.

I attended a symposium last week at NRC on this problem and I was tremendously impressed with the amount of work that is being done, and the amount of information that has been accumulated but I was more impressed with the complexity of the problem and the care of thermal burns, and I certainly am convinced in my own mind that there just is no simple treatment for the problem of thermal burns.

I thought the one good cheerful note in the whole thing was the use of blood substitutes. We had a man from Sweden and one from Scotland and several from England and apparently they are using dextran, and it looks, I would say, quite promising along these lines.

I think the one big problem that we have and the one becoming more acute and the one which I feel we do not have the answer for, is the reaction of the soldier to ionizing radiation. I believe it is becoming

more acute because I think that the use of the weapon as a tactical weapon has now gone beyond the realm of possibility and into the realm of probability.

Now, we have lots of experimental work on animals and we have lots of cases of whole body radiation treatments, but all of them in patients and we have no controls and we don't have anything that we can put our finger on.

A few years ago I asked the radiological society of North America to give me the answer in this problem: How much ionizing radiation can a healthy soldier take and still perform his duties? They wrote letters to every radiologist in the country and received six replies as to patients who had received whole body radiation. Most of this work was unsatisfactory because the data was very poor. I don't believe we can go too much on our Hiroshima and Nagasaki studies because there are so many complicating factors.

Dr. Edward Everett brough out an interesting point in his thermal work with dogs, and found out that aslittle 100 R to a dog with 20 or 30 per cent body thermalburn is very, very important, and so I think the data from Hiroshima and Nagasaki is colored. There were thermal injuries in poor states of nutrition.

Now, at every conference I attend of the military, I am asked by the line officer how much radiation can a man take? I tell him what I think, and they they ask me where I get it, and that is where I fall down. I tell them that I think men can take 100 R.

Well, as a result of this conference in San Francisco, we found that one question that was asked was how much ionizing radiation, an acute dose, will be required to put an individual out of work in so far as the army is

concerned. The answers varied from 800 R to 25R, and 300 R by Templeman and Cooney, and 25 R by Dr. Portman, a very outstanding radiologist.

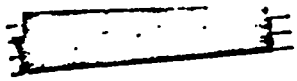
At our meetings we will have one doctor in the service get up and say that you can take 100 R, and another doctor in the service get up and say, "I know that 25 R will make patients sick."

So we are very much in a quandary and we have a responsibility that is tremendous. If this weapon is used tactically on a corps or on a division, and if we have, say, 5,000 troops who have received 100 R radiation, the Commander is going to want to know from me, "Is it all right for me to reassemble these men and take them into combat?" I don't know the answer to that question.

Now, I can't see that we can statistically prove it, and I don't believe we can take enough of normal well patients and give them whole body radiation so that we will prove anything to the statisticians, but I do feel that if we had 200 patients that we could say, "We have given these people 25 R, or 50 R, or 100 R, or 150 R," I would be willing to stop there and say you did or did not affect them.

I think psychologically it would make a lot of difference to the soldier if we were able to tell him that, that this is a little different than any weapon we have used before, and they realize the machine gun and the other type of thing, but they don't realize what this is, and if we can assure them that we have something pretty good to put our finger on, I don't believe that otherwise we are living up to our responsibility.

Personally I see no difference in subjecting men to this than I do to any other type of experimentation that has ever been carried on. Walter Reed killed some people. It was certainly the end result that was very wonderful. Shall we wait until we find out and force people and force



thousands of yound men perhaps and maybe lose the battle as a result of not knowing, and so on?

We force people to crawl through the infiltration plants for a purpose, and in doing so many of them are killed and we had some killed just last week. I think that we have a very definite purpose in mind here, and I personally feel it is our responsibility and we should make an effort to try to answer the problem.

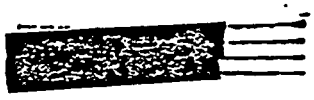
I feel that we can get volunteers both officer and enlisted to take up to as much as 100 R and 150 R, whole body radiation.

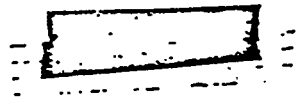
DR. GREGG: Thank you, General Cooney. I think that I'm right in understanding that when you say that the effect on troops, you mean the relatively quick, within 24 hours effect, or do you mean the whole spectrum?

GENERAL COONEY: The problem that I cited is that we have a large concentration of troops, and we have an overhead burst and we have 10,000 men who have been subjected to, say, from 25 to 150 R, and the Commander wants to know are these men going to be fit to go into combat, and shall I leave them here, or shallI send them home. I don't have that answer for him.

DR. GREGG: Dr. Powell, do you have anything to add?

GENERAL POWELL: I would like to say that was one of the main things that I was interested in, that has been presented by General Cooney. That is what we are all faced with, the answer that the line personnel want to know, and they have now of course enough knowledge of this that they are able to talk about it, and it is the same story when they get the doctors together, one has one answer and one another. It is hard for them to analyze how we can come up with such wide answers.





However, I was not quite aware of the exact nature of this meeting and maybe the extent of the things that we should showinterest in, and for fear that I might pass over something that we definitely do have interest in, as specific thoughts, I would like to just go over what I have drafted up and I think the program has been well covered, and I don't see how any of us can afford to not be interested in every phase of it, because we never know what particular phase we may be caught in.

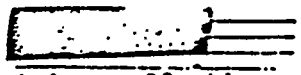
Of course, we all have specific interests, but we may all be victims of some particular phase that is not primarily what we are thinking about. We certainly are aware of all of the fine work that is going on in the fundamental biophysics of flash burns. A recent symposium wasjust held here and certainly it is evidence that you have sufficient work certainly going forth, and we hope that it will continue.

There is an additional study in the fundamental mechanisms as to what produces the tissue injury and the tissue response to the effect, and any other knowledge fundamental to the problem of protection and treatment.

Protective devices against thermal injury and radiation are important. That is the clothing, masks, gloves and so forth for the protection of the individual and for further development of precipitators, filters and other items of this type.

A valuation of prophylactic and therapeutic agents for ionizing radiation injuries by the study of human patients—in other works an extension of studies now being carried out on patients receiving regular therapeutic radiation.

We are interested in the effects of different combinations of blasts, thermal and ionizing radiation injuries, with respect to prognosis, the immediate clinical picture, segregation and selection of patients for selective treatment.



The evaluation of the minimum effective measures for the initial care of mass atomic warfare casualties—this could be followed by development of training material or self-help, ordinary first aid and the value of extraordinary first aid extended over a matter of hours or even days.

Individuals we feel must be prepared to do much more and for a longer period than our present concepts of first aid imply. The differential effects of local shielding as a protective measure against ionizing radiation is important.

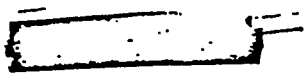
As to the personal decontamination procedure, simple and rapid improved methods are needed, and also needed is a better doctrine for the treatment of contaminated in-take skin and contaminated wounds with some determination as to when this treatment is an emergency and when radical treatment should be considered.

There is the problem of the disposal of decontaminating materials which become contaminated, and the design of treatment facilities for the contaminated wounds. That is the problem that we think needs further study.

In the field of developmental items, and facilities, there is continuous simplification of field radiological facilities and reduction in the number of replacement parts. The ones that we have now are certainly very prone to get out of fix very readily, and certainly require an awful lot of maintenance.

Decontamination equipment: Airborne radiological and analytical laboratory. This airborne laboratory should be able to do accurate analysis of samples from the nose and desk tops.

Water analysis for the identification of the radioactive material,



particularly aimed at chemical precipitation of the radioactive matter, and that should be one of the functions of such a laboratory.

There are a few other items that we think are of maybe alittle more urgent need or interest, and that is the estimation of the maximum medical load with the minimal essential treatment. In other words, an estimation of hospital capabilities factors we feel are needed for the estimation of the maximum medical load with minimal essential treatment that can be rendered to mass casualties of atomic warfare catastrophy.

This should be in terms of so many patients per day per so many hospital beds per so many hospital staff. Further factors may be necessary for the different combinations of the blast, thermal and radiation injuries.

Reliable human radiation dosage tolerances. That has been well covered.

Components and recommendations of the AEC on film badge dosimeters. It must be recognized in the military operation that they are not as simple as desired.

We have been particularly interested in the proposal, I believe, that is from the Poloroid Company, and a new device that we certainly have high hopes for due to the simplification and being able to read it directly.

The re-evaluation of the inhalation hazards for air crews in atomic warfare operations--although the hazard of the cloud has been studied by the medical services, the confirmations of their finding we believe are indicated.

Technical medical information. We believe that there is still need for more technical manuals and more technical medical training films and slides and other training aids, particularly for the medical personnel.

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I believe probably some of that is not particularly applicable, maybe, but I was afraid that I might lose out and I might forget some of the points that might still be of interest and perhaps some of that is covered.

DR. GREE: That is helpful, thank you.

Now, Dr. Warren, have you got any comment to make on any of these questions?

DR. WARREN: There are several of real interest. I think perhaps one of the central ones is this question of the calculated risk or the tolerance of the human. There are a number of problems that come up in relation to a determination of this sort. Admiral Greaves has called attention to the various problems raised by fatigue, work and so in in the same individual. That is of course paralleled by some of the Rochester observations on experimental animals that are being worked in a tredmill, as against those that have an opportunity for a rest.

I would like to go back to one of the remarks made this morning in relation to sociology, that sociologists sometimes forget that humans are pretty much like animals, in a good many ways. We have an enormous amount of animal data. That is animal data that we have been trying to accumulate and to tabulate over the years. There was the Army project at Hopkins that you will recall, General Cooney, that gathered some information. There was an effort by the NEPA project to gather up known information, and there is the survey of the radiologists that you mentioned and other types of things.

We are engaged presently in an attempt to get together all of the animal data for various types of radiation, and review it as carefully as possible, and see where the general picture seems to come out. There

are two very important things about it, the animal work that we have definitely bearing on this problem. One is the fact that very fortunately the radio-sensitivity of various species of animals tends to fall on either side of that of man. We have the extraordinarily sensitive guinea pig on the one hand, and we have the relatively insensitive rat on the other hand. In fact, if we want to go to the best of all, we have the cockroaches that lived so nicely on the Japanese vessels at Bikini.

The problem of getting adequate numbers for statistical significance is very great. I think General Cooney's comment in relation to the estimates of the radiologists is extraordinarily pertinent in this regard because I don't suppose that there are half a dozen radiologists in the country that have seen an acute death from radiation, and yet every radiologist practically was ready to stick his neck out and estimate how much it would take to kill.

One of the reasons for the extraordinary complexity and confusion that exists is existing in this field because a good many radiologists who have not earned a right to an opinion have nonetheless expressed that opinion very loudly and very vociferiously. That has helped to confuse the issue very, very materially.

We have learned enough from animals and from the humans at Hiroshima and Nagasaki to be quite certain that there are extraordinary variables in this picture. There are species variables, genetics variables within species, variations in condition of the individual within that species.

I think that it might be almost more dangerous or more misleading to give an artificial accuracy to an answer that is of necessity an answer that spreads over a broad range in light of these variables—it might be worse to give a suedo accuracy than to state things in terms of a range.

I think General Cook [illegible] with me that — LD-50 for the human as 400 R, there are certainly some individuals that will die with as little as 200 R, or possibly some with 700 R.

Now, there we have an enormous spread relatively speaking to the LD-50. Suppose that we have the situation where a group is irradiated and they are told that with 50 R nobody will be sick and some of them get sick. Confidence is gone just as badly as though they had been told no information at all.

I think that we have got to be careful that what we say isnot narrowed down overly excessively because we have to talk and our knowledge of susceptibility of other types is such that we know that there can be enormous variations in susceptibility to digitalis. We have seen the problems that have come up with the sulfa drugs and so on, and radiation is no exception to that point.

In order to get a satisfactory answer to this problem in humans, I don't see how it is possible to have an answer that means anything, over and above what we already have in our animal data and our scattered human data, without going to tens of thousands of individuals.

I have tried to get good statistical help on this problem. That at once puts in the question of, "Is such a thing practicable?" If we were considering things in the Kremlin, undoubtedly it would be practicable. I doubt that is is practicable here.

Another point that I think would be worth while calling to your attention, and I would like your judgment onthe question of how far would we be warranted in considering results of primates of significance in relation to the human problem, if we had a spectrum running throughout the warm-blooded animals up to man, together with a scattered clinical

observation that we have in man on the one hand d the observations in Japan on the other.

How closely we could possibly come to the answer is aproblem. I would not be quite honest in saying what I am s a ing if I were not to add that personally I am very much opposed to human experimentation when it isn't for the good of the individual concerned and when there is any other way of solving the problem.

I think that General Cooney's citing of Walter Reed's experiments are very much to the point. On the other hand, I think it needs to be remembered that there was no known host that could be used for such experiments, and no way of carrying it out from the standpoint of the known bacterial or virule effects. There was no way of fulfilling the postulates because there was no other way or no other animals than men to be susceptible.

Those are some of the things that I would like to toss out.

DR. GREGG: That is very good.

GENERAL COONEY: I agree that statistically we will prove nothing, but generals are hard people to deal with, and if I tell a general that "Your men might get sick with 50 %," or "They might not get sick until they get 150 %," that is a very unsatisfactory answer for him, and he will not accept it.

I don't think that we are interested in pushing this thing to the point of finding lethality but I do believe if we had 200 cases whereby we could say that these men did or did not get sick up to 150 R, it would certainly be a great help to us.

DR. WARREN: I wonder if it would really be a help if it came to the final analysis. I think that there are two other things that need

to be thought of in relation to this. One is ho accurate are such measurements going to be in the field, and, two, how important are the objectives going to be? I can think in terms of times when even if everybody on a ship was sea-sick, you would still have to keep that ship operating.

ADMIRAL GREAVES: I am very glad that this question of human experimentation has come up in the open so quickly and so frankly. I certainly agree with everything that you have siad, Dr. Warren, and I appreciate the idea of human experimentation within this country is certainly repugnant.

This has come out before, as you know, and it came up at the National Research and Development Board not so very long ago, and it was threashed out there, and it went just about like this discussion is going here.

We don't like the idea and we have got alot of data from irradiation of patients for various diseases that they give radiation for, but the question always comes back to this: Can we unite those results to what our problem is?

We have aproblem to answer, the same thing that General Cooney says. We are going to have it if we have this type of submarine that we are talking about. The Air Force is going to have it if we get that kind of stuff in their planes, that is that type of power in their planes. That is that type of power, and just where and just what can we tell these people as to what is safe and what is not safe.

Now, the question that you brought up about the value of using primates--well, you mentioned on one side of the human line we have the guinea pigs, and the other side we have the rats. We don't know, as far as I know we don't know what the results would be in that event. I say,

maybe it would be. I think our position in the matter of human experimentation is the same as everybody else. We don't want to do it if we can get out of doing it, but if that is the only way we can get the answer, that certainly is going to be more economical in the long run to take a few chances now and perhaps not lose a battle or even worse than that, and not lose a war.

DR. WARREN: I think that there is a great deal in that, assuming that there is the set of consequences that you propose, and also assuming that accurate answers can be obtained. I think a lot of this is a matter of presentation.

For example, I am not at all sure that the data obtained from 200 individuals radiated under known experimental conditions is going to be any more accurate than the data on 200,000 individuals that have been irradiated under non-experimental conditions.

We have a very major amount of information, complicated by various factors to be sure, but nonetheless with a very large number of individuals involved, that help to compensate for some of the variables that come into the picture. I would be inclined to take the viewthat we already have a considerable amount of human data to provide us land-marks for orientation with regard to the human.

By and large what we usually do in solving an unknown problem in a field such as this is to do a lot of experimentation in animals, to build up our quantities, our knowledge there, and then get some cross-checks to the human.

I have believed so far, at least, that it is feasible for us to get these cross-checks with existing knowledge and by closing with more and more species of vertibrates in on this general picture of the human.

I think that if we had not been quite so honestly scientific from the start, and we had said when the question was raised by officers in the line, "Yes, we know definitely that you can take 25 R without anything happening," I am quite sure that that is accurate probably within a tenth of one percent, if not accurate within 1/100 of one per cent, but we were hesitant perhaps to say it flatfllotedly because we weren't absolutely 100 per cent accurate.

We can say, I think, with a good deal of certainty that we know that 25 R is safe. We know that an appreciable proportion of any group of individuals will be seriously ill at 200 R, and that some will die at 200 R. We can say with a fair degree of assurance that with 100 R, other casualties such as burns will be materially complicated and the lethality of minor injuries will arise, and there is a great deal of permanent damage that is done to the organism as well as transient damage at the 100 R level.

I wonder if we were to stick to those brackets, if we weren't pretty nearly reasonably accurate, and if that isn't as close as we ought to come. I remember very well when they first put out French 75's in the last war, some enthusiastic ordnance officers got down to a factor of safety of two. Well, that meant that a fair number of the gun burst, and the morale at the artillery training camp, Camp Taylor, was pretty darn low for a while on the basis of that.

I don't think that you can skirt too closely to your factors of safety, and to try to narrow it to say that 75 R willdo this, and 100% will do that. To my mind that is skirting awfully close to your factor of safety, even if you had absolute knowledge in the field.

GENERAL COONEY; I agree with you thoroughly, Dr. Warren, and I

quote the figures just as you have quoted them to groups of military people. But they say, "Who are you when another man stands up and takes the other side?"

Now, if we could get a group of prominent radiologists or prominent doctors and this is what I have been trying to do for years, and I have been so unsuccessful in doing it, if we could get a group of prominent doctors who would say, "Yes, this is it," and if we could give that to the military, we are perfectly satisfied. Up to now we have been unable to do so.

DR. WARREN: I wonder if you could not do that if the doctors who knew would be the only ones who talked. It is the doctors who don't know who confuse the issues because they want to talk, too.

GENERALCOONEY: That is our problem, doctor.

DR. GREGG: General Cooney, you have made one suggestion that interested me very much. That was the point of getting volunteers. Now, I am interested in that principally for this reason: I think that there is enough of the general atmosphere around the AEC affairs that it is singularly important for us to stear away from hum an experimentation because we never could get, or certain things could not be brought out in the public trial, which is a control.

GENERAL COONEY: I agree with that thoroughly.

DR. GREGG: So this question of volunteers interests me. I am ignorant of a good many examples that you may know of mass volunteering on anything. What kind of things can you tell me about that?

GENERAL COONEY: We have never had any trouble in the services in getting volunteers from the time of Walter Reed to the present time. You can always get certain soldiers and officers to volunteer for virus work,

as has been done, for malaria, or for many things. I think if the problem is stated to them honestly, giving them all of the probabilities, you go to a port of embarkation of troops getting ready to go over to Korea, you would have no trouble whatsoever.

Maybe that might not be the point to get it, but it could be very easily done there, and I am sure it could be done in many camps.

You can evaluate this problem and tell them that perhaps it won't be the answer, but it seems to me that we could do it under voluntary measurements rather than involuntary measures when the man has the uniform on and we have to find out, and this way is a much more democratic way of doing it.

DR. GREGG: It is.

GENERAL COONEY: I certainly agree with you. I don't believe that the Atomic Energy Commission should enter into it, and I don't believe that they have any problem. I think it is just until the bomb goes off. When the bomb goes off then the problem exists, and it doesn't exist now to the Commission. They are not faced with this problem.

But we are very definitely faced with it, and if you can get me ten prominent doctors in this country to say just what Dr. Warren has said, so that I can give it to the military, and say "This is it," that is all that I ask.

DR. WEARN: I would like to think just for a moment as to how you could get this experiment up, assuming that the volunteers could be had. Now, the difficulty with observations in the past is that some of them have been fatigued, some of them have been burned, and some of them have been tired, and some of them have been under-nourished.

Would you take your 200 men and have them allat rest, or would you

have some of them tired or would you have some of them wounded, because that is the circumstances under which your men will be.

GENERAL COONEY: No, sir; I wouldn't consider any wounded or any burned or any tired. I am thinking merely of a situation where we are making an amphibious landing, and there is an air burst and a certain number will be wounded and a certain number will be burned and they are casualties and they are already out, and a certain number will be sick from radiation. But there will be a large number who will not be. Then the commander is going to say, "Can I use these men and how long can I use them?"

DR. WEARN: Some of these men will be tired, and some will be exhausted and some willhave lost their lunch going ashore and there will be a number of others.

GENERALCOONEY: That may be before the thing starts, and I am thinking of Normandy, and the night before Normandy.

DOCTOR WEARN: The emotional situation within the men would be there. I can't conceive of those results being of any greater value.

GENERAL COONEY: You mean than psychological?

DR. WEARN: If that is so, who is going to give an answer and stick by i

GENERAL COONEY: We can tellthe commander that we have done this on 200 healthy individuals and that none of them got sick up to 150 R, and that they would be all ready to carry on, and that seemsto me would be something, or we can tell him that they are allsick at 100 R, and he had better not take any of his men who have 100 R, they are out. That is very significant. If it is 50 R, that is important. I don't know.

I quote all of these figures and tell the people, and then another officer gets up as it happened at ameeting over here the other day with a large number of line people, and they said that that is absurd, it is

[redacted]

ridiculous, and they said, "I know that 25 R will make a man so sick that he can't carry on." Somewhere are we?

DR WARREN: That reminds me a good deal, General Cooney, of the situation we frequently have in court when two psychiatrists who have no idea of whether a man is sane or not, when he made a will, and they are being called and are equally positive that he was sane on the one hand and insane on the other.

That is one of the reasons that lay juries have learned not to trust medical testimony. I think that you would find with your experiment on these 200 men that the same doctor who said that 25 R would make them deathly sick, would still be saying it, because I have presented one for many years with figures on irradiation of the breast and he paysno attention to it, and he goes on exactly saying the same thing that he was saying 10 years ago.

GENERAL COONEY: Actually we would still have it on paper, and we don't have it now.

DR. WARREN: Actually we have got the results of an enormous experiment. We have the experiment involving over 200,000 people in the Nagasaki and Hiroshima areas, and I think that those results are real. I was in there, and I saw the people when they got sick. I know that one can get reasonably accurate calculations as to the amount of radiation that they received, and they can be placed pretty accurately within the buildings.

Harry Bowman has figured out for us the amount of shielding that some of them received.

I think that we have not made the most of some of the evidence that we have available, and I think perhaps we have been a little too tolerant of some of the radiologists who are arm-chair experts rather than practical

[redacted]

experts in this field.

GENERAL COONEY: Well, I think that is very true, but I think on the other hand that there is a tremendous number of complications in the data when you evaluate it.

For instance, you and I know that it requires 350 R to ebelate a man with 100 KV, and as our intensity goes up it requires more and more. I have a Weapons Effect Handbook which shows me that you get 25 R at 2,000 yards, and yet our Japanese data shows that we have patients epilated at 2,000 yards. So I am completely confused. I can't understand how it can happen. You epolate a man at 2,000 yards with energy such as we have from the fission bomb.

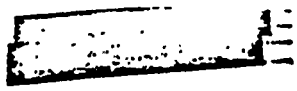
DR. WARREN: There may be some confusion there with the flash burn epilations. That is one of the problems.

GENERAL COONEY: That is true.

DR. WARREN: That is one of the problems that has to be weighed and brought in.

GENERAL COONEY: And I think maybe sickness or illness is there, but there again we have got to have that. If we can get ten doctors to evaluate that for us, and to come up with an answer, then we would be satisfied. If we don't get that, it seems to me that we have a responsibility which we do not have the answer for.

CAPT BEHRENS: IT seems to me that you are talking about experiments involving dosages, with an idea of getting a rough approximation to operational efficiency or capability, and it seems to me that it is not quite in the same category, even, as the experiments that were originally done by Walter Reed, which were really involving a serious threat to life.



Now, what we are proposing here as near as I can tell, does not involve any threat to life or any serious threat to health. What we are trying to get at is an idea of a rough approximation to the operational efficiency that you could expect and which would so to speak document it a little bit when you present it to the admirals and the generals and the captains who have to take their people into battle under such conditions.

I don't think with the dosages proposed that there is a great deal of danger or any danger at all, and that perhaps that might alter the way we feel about it.

We are after a rough approximation of operation of efficiency, and what we might expect from morale rather than looking for facts as to how we would deal with serious irradiation illness.

As I understand it, the idea is to stop considerably short of where they get serious radiation illness that would threaten the man's health or life very seriously.

DR. WARREN: I think that I would feel very reluct[illegible] into this in the light of the animal data that exists, to have 100 or 150 R.

We know that it does materially shorten the life of animals and I would expect in the light of all we know that it would do so in the case of man.

Dr. GREGG: There is one stop in the so-to-speak procedure, or the sequence of events, which I want to ask a question about, and it might sound flippant but I don't intend it so, and that is this: Supposing you were to expose 200 men to purely experimental conditions, and give them dosages of 50 R. Let us assume in that 200 there are 75 who at least have some complaints, and among them we will say that there are 25 who have pretty serious disturbance. Are you able to judge whether

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the symptoms of the men are such symptoms as a line officer could or would disregard anyhow because there is a gap there?

What is your line officer going to override? If you tell him most of the men were seasick, I suppose a good number of them were in Normandy, too, but they had to fight and they had to callon themselves for efforts that were away beyond what you get if you just say "How do you feel?"

Do you follow my line of questioning?

GENERAL COONEY: Yes, sir: I do, but my thinking is a bit different. What I want is this: I have a responsibility to the line officer to tell him whether or not these men are going to be able to fight. I tell him that he has a division of men, we will say 15,000 men who have received up to 100 R. I say "Go ahead and take them, take them into battle." If he gets them into the battle and half of them become ill the next day, I have not answered my responsibility or lived up to my responsibility in evaluating that hazard for the fineman.

We take them into a malarial district and we know the hazard and we are able to evaluate that and we know how to take care of it and we can advise them, that such and such apercentage of your men if they take atabrine are not going to get it or they will get it, and he knows how to prepare his campaign. This way he doesn't know how to prepare his campaign because we can't even come close to giving him an answer.

DR. GREGG: What you are tellin him is that the men under those circumstances will be unable to fight.

GENERAL COONEY: They will be unable to fight, sir, that is what I want to know.

DR. GREGG: That defines it much more closely.

GENERAL COONEY: That is exactly what I want to tell him, that they

will or will not be able to fight.

DR. STAKMAN: I would like to raise a question, not a medical one, but an experimental and statistical one. Could you possibly get the information that you want with 200 men? I don't think you could. I think it would be 2,000 would be nearer, and you have got to given them different dosages and you have got to replicate the experiment a number of times.

If you use the same men for the different dosages, you are piling it on. I think that you would have to think in terms of far more than 200 men.

GENERAL COONEY: I say statistically it is impossible, and it is not even thinkable, but isn't it better to get some idea with a few men than having to take a chance on the others? Would you send a group of men into an area in which they would get 150 R tomorrow, even if it is a very important area?

DR. STAKMAN: The only thing I am saying is that if you are still guessing, or your stituation is extrapolating from small numbers to larger numbers, and your extrapolating from small numbers on to large numbers that are going to behave differently presumably than they are now, all I am saying is that if we are thinking in terms of experimentation then we should have large enough numbers so that the data would really be significant.

DR. GREGG: I think the answer to the man who says, "You doctors all disagree," is to say "Yes, and we will probably until it is necessary to try this experiment out on five or six thousand people. That can't be done.

There is a chance that if 200 dozen show you somethin, ahigh range of reliability, there is a perfect chance that you may be wrong when you say, "Yes, they can fight," and then it would end up on you just the same,

because they couldn't. You might be wrong on the wrong side.

GENERAL COONEY: I well realize that, but it seems to me we ought to have alittle something. We can say, "Well, all that we have is the data on 200 men, and here it is," and that is something, but when I start talking about animal experimentation, as one general said to me. "What are we--mice or men?"

DR. WARREN: I think one of the things that is very important is that we are in part mice, and only in part men. There are a great many attributes of the mouse that we still have, and we can learn a great dealfrom what happens to the mouse and carry that on. There wouldn't be any point in any animal experimentation if we accepted that assumption.

DR. GREGG: You have to admit the point that some of us are rats, too!

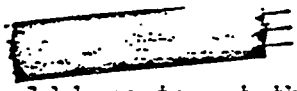
GENERALCOONEY: Nevertheless, we have a problem, which we do not have the answer for, and if there is no way, if this is purely illogical, then we would like to have someone tell us. We only ask for some backing of the medical profession.

DR. STERN: I would like to follow up Dr. Stakman's question--how great is the difference with rats and mice, and do we need a group of 200 people divided into three groups of 70 people? How is the spread in experimental animals.

DR. WARREN: In the various species, take mice for example, you can get a variation of approximately 200 R on the LD-50 just by a change of diet, or a change in conditions in the animal house.

DR. STAKMAN: You see my point too is that you are going to try them at different exposures, and it wouldn't befair to take those who had the lower exposure and try them right away on the higher ones.

DR. STERN: That is why I said three groups of 70 each.



DR SELLERS: And you would hope to get them under all of these conditions. That is all that I wanted to say, and I am not arguing as to whether this human experimentation should be done or not. If it is done, I should think that it would be done by the armed forces, but I am simply saying that I think that we have got to think in terms of far larger numbers than 200, to get data that would be really reliable.

GENERAL COOKEY: I agree with that, there is no question about that.

ADMIRAL GREAVES: There is another question that Dr. Warren has just touched on, that I think probably would be of interest. You mentioned the fact that from the animal experimentation that is available, you would hate to submit yourself to 150 R, because in the animals it isknown that life is shortened. Well, the type of experimentation that has been discussed so far is pointed toward immediate results and the type of people who would be subjected to that experimental work would be people you would have to control over a relatively short time. You would lose control.

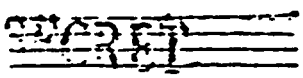
But when this subject was broached first by NEPA they proposed doing the work on long-term prisoners, people who would be under the control of observers for a sufficient period of time so that the kind of results that you mentioned would be available.

Well, that type of experimental work is a little difficult for the armed forces to engage in.

DR. GREGG: Is this civilian prisoners, you mean? Ad. Greaves: Yes.

DR. GREGG: Doesn't that fall in the category of cruel and unusual punishment?

ADMIRAL GREAVES: Not if they would carry out the work as they proposed at the time they proposed it. It would be on an absolutely



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volunteer basis, and under every safety precaution that could be built up around it. I don't think so, and it didn't strike me as being cruel and unusual.

DR. WARREN: It is not very long since we got through trying Germans for doing exactly that thing.

ADMIRAL GREAVES: That wasn't voluntary when they did it, they made them do it. I think that there are a lot of prisoners and I am given to understand that there are plenty of people in our prisons who will volunteer for that kind of work.

DR. WARREN: Always for a quid pro quo.

DR. WEARN: Prisoners were used during the war, as you know, for plasma and blood substitutes, on a volunteer basis, and some in the Massachusetts prison, and all of them expected to be released immediately, and asked to have their cases put before the parole boards right off. It wasnot that they had any promises and indeed it was made clear that there were no promises, but as a result of that they expected to be released.

DR. STAKMAN: Mr. Chairman, may I ask another question. What are you going to do when you are asked for a categorical answer to a question to which there is no honest categorical answer? Are you going to be dishonest?

I mean, after all, all of xx us would have to give these values in terms of ranges. You couldn't give any absolutely flat figure. This isn't the elasticity of steel at a given temperature, with agiven force applied to it, and that sort of thing. You are dealing with a heterogeneous biological population, and I don't think that you are ever going to get an answer.

You have always got to have a range, do you not. I would just like to raise the question as to whether the range isn't sufficiently well known now so that these people who are in difficulty can do nothing but be scientifically honest and say, "Here is the range," and here are some of the factors that affect that range, and there just isn't any precise answer to that.

I just can't see how that can be done. I mean dealing with any biological object, you have got hetergenity and you have degrees of probability as a result of large numbers and frequent replication. I don't see quite how you can get it better than that.

You would have to have large numbers to get it more precisely and a large number of conditions, and a good deal of replications because there is always that in all of this type of material, and there are a lot of imponderables.

GENERAL COONEY: Suppose that there is no answer to the problem, and could we get a group of men to agree with us on that?

DR. STAKMAN: It seems to me that that is about the best that you can do.

ADMIRAL GREAVES: The way it is now, we don't know for sure whether we know why we don't have the answer.

DR. STAKMAN: That is right.

ADMIRAL GREAVES: It may be that after this work is done, we wouldn't have the answer but we would know why we did not have the answer.

DR. STAKMAN: That is right.

DR. GREGG: I would like to explore one other thing that General Cooney said, that involves something that you also referred to, Dr. Warren.

I know that my own personal first move in a thing like this would be

to go out and look in pretty carefully the experience and general reasoning capacity of the doctors giving such extremely different answers. I wouldn't be satisfied without finding out whether those doctors that gave extreme answers on the other side, gave me the general impression of being reliable people or not. Or whether the persons who for a lot of different reasons I began to have some confidence in, came somewhere near to an agreed figure.

I see your point and I have the same sort of thing sometimes with my own board, and they say, "You doctors don't agree so I guess there is nothing in it at all," but I can get abetter concurrence of opinion, we will say, on a case of cardiac failure from five really good men who are cardiologists whom I know are good cardiologists, and I will expect a larger measure of concurrence there than I will if I send out a hurry call for people who call themselves cardiologists and then take down their opinion.

DR. STAKMAN: To put it in legal terms, you want to know something about the credability and reliability of your witnesses?

DR. GREGG: Yes, and I think the width of their statements would be narrowed substantially as soon as you sorted them out. Now, that is only my first plus reaction to it. Does that make any sense to it?

DR. WARREN: It makes very real sense.

DR. GREGG: Where do you think that their answers would lie?

DR. WARREN: I think that it would lie quite closely in the group that have had real experience in this field, and I think General Cooney and I for example see very closely eye to eye, and I think that the views that Dr. Hemmelman has, and that Colonel Decoursey has, they are very closely paralleled to ours.

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And I think that those who have had first-hand experience, that have seen autopsies on cases, that have cared for ill patients, are in pretty general agreement.

It is the ones who have had to deal with the nebulous psychological factors of when a patient is going down to the x-ray room for treatment and starts to vomit.

I remember very vividly the question of radiation sickness came up in our own hospital some time ago and we suddenly began to get a lot of grief when we hadn't been getting any with dosages which were pretty standard dosages. In looking into it a little more carefully, we found that all of the patients who got sick came from one floor of the hospital and inquiring a little bit we found that the head nurse on that floor, a very sympathetic and well-meaning gal, had somewhere gotten the idea that the use of carbohydrate would prevent sickness and she was going around to these patients before they went to x-ray, and saying, "Now deary, you are going to have an awfully bad time down there, and you are going to be very sick and here is some nice Caro syrup, and if you drink a glass of this and get x-rayed, you won't be sick at all."

Well, they went there psychologically prepared, with an up-set GI tract, and it isn't any wonder that they were sick when it happened.

GENERAL COONEY: I think the whole thing sums up to this, that we in the military are your public servants and if American medicine fails, are we properly discharging our responsibilities. That is all we wish to know, and if some group, some prominent group would tell us, if you have done all that you can on that, then we are certainly very willing to accept it.

DR. STAKMAN: May I raise this question: I think that this is awfully

important, Mr. Chairman, in many respects, but is this correct? That about the best you can do after everything that has been said here, in a situation like this, is not to get a categorical answer to a question that cannot be answered categorically, but to get a concensus of the most competent people with respect to the range and then that is the best that can be done, unless you want to go into large-scale experimentation.

DR. GREGG: Yes, that is right. I would like to ask our friends from the armed forces, whether for lack of something better as a basis, it would be in their opinion worthwhile for us to try and get a commission's opinion of this kind, so that they willnot be subject to random comments on the part of various radiologists here and there, that add up to the simple statment, "Oh, but that is ridiculous."

I don't think it is reasonable or fair for you to be exposed to that kind of gunfire from all over the landscape, and I don't see why we couldn't take measures to get an ad hoc commission for this and give us an opinion.

GENERAL COONEY: That would be a great help, Dr. Gregg.

DR. GREGG: I would be furthermore inclined to think that we would take that and if it added any guilt edge for us to transmit it to you as an ad hoc commission that we had appointed for that purpose, and if we could do that so much the better.

As you can see, most of us are awfully leary about giving enthusiastic approval to a mass-scale experiment which as Dr. Warren has stated, he feels there is relatively great difficulty except in bracketting to give a categorical answer of the exact number available. From what I know of this world, I would be extremely dubious if it all came out at exactly 74 R. Human beings being what they are, they aren't that way with atabrine

or any skin lotion that I used when I was working in the outpatient department in dermatology and so on.

So I would think that you would have to get some kind of an expression of the best available opinion, and if it would be of help I think we ought to consider it very carefully.

GENERAL COONEY: I think that that is wonderful, that is what we have been trying to do for a long time, and we have been unable to do so. It would be very much appreciated, Dr. Gregg.

DR. GREGG: Well, now, I think with that we ought probably in the light of the time limitation, to go on to the next item, and before that I simply would like to say that we are very glad to have Dr. Smith add Dr. Glennan with us and I am going to reverse the order of the next two items and let us take No. 5 before we take N. 4, and No. 5 is the general status of radiation instruments brnach and Fort Totten activites.

DR. GREGG: Well, now, gentlemen, I disclaim [redacted] responsibility for the selection of the next number on the program. Dr. Warren thought that you might be interested in some of the general impressions that I had of the present state of medicine in Europe, and I am going to go fairly fast and I will guarantee to be through at 5 o'clock.

First of all, as the base line for these comments, I would say that I lived in Europe from 1924 to 1931, visiting all of the countries except Turkey, I think, and including Russia and Iceland, at least once and a number of them a great many times. Then I went abroad about once every two years until the war, and I have been over four times since the war.

I think the first generality that is valid about medical education and studies in biology in Europe is a generality that you can make about Europe itself, and I got it in a curious way. A friend of mine used to turn up in the Paris Office and say, "Well, how are things in Europe?"

Well, I learned through that question that the United States is probably the largest single homogeneous area in the world, both in space and in time. And there has never been such an extraordinary homogenetite because that question meant that they had come from a country where somebody who lived in Ohio could answer for what was going on in Minnesota, roughly speaking.

But you can't do that in Europe at all. If somebody said, "How are things in Norway?" there is an answer to that, but it isn't valid to cover Italy also. It varies tremendously. The variety and tradition and the variety in the language and the variety in economic position--there is variety also in history.

I think one of the strong impressions that I have gotten out of Europe and it is just as clear now, is that they are tremendously more controlled by and influenced by their traditions than we are in this country. We don't have any very strong historical perspective in this [redacted] I can remember going

to one of our Southwestern states and asking why a medical school had the position it had, and the answer given perfectly honestly was, "Well, we have been here for twenty years." Well, they are going to be there for another one thousand years, but already the twenty years seemed to them to be a very old story. And that is in sharp contrast with Europe.

Another thing that impresses you, and it is in line with the tradition, is that Europe still shows and it shows in higher education, a pretty strong feudal tradition. It is the people that matter that get to the university, and that the people that get to the university ordinarily end up making some considerable difference.

That is also shown by the fact that the people that get to the university in a European state in the main are far smaller proportions of the population than is true in this country. In the mid 30's, six times as many Americans got ABs and BAs as in England, relative to the population. That means that if we take a selected sixth out of our ABs and BSs, they would make a reasonable comparison with the graduates in Britain.

Education is an upper class thing also because the ruling people in government have usually been to the university and the governments don't have to do flip-flops and handsprings in order to get the attention of the government.

It is a pretty steady continuing understanding among gentlemen that the university will have a certain measure of support.

Now, I have got to qualify that later, but that will come. State support is a pretty fixed affair. The result of that is rather interesting, and I think has some moral value for us, and that is that the Europeans take the size of the budget as a pretty nearly fixed affair. They then spend their attention saying what is the best thing we can do inside this amount of money, and we in this country are a little bit inclined to say, "Well, of course the

budget is there, but maybe we can get an increase so why not do something additional?"

We don't put quite as much attention on the quality of what we are doing, because if we want to do something that has a big popular appeal, we will go out and get one of these foundations or the government to pay the bill for us.

The Europeans are very much concerned with what the mathematicians would call an elegant utilization of their time, more so than we are in this country, and you are struck by that continually.

Now, in that semi-feudal regard for the intellectual that shows itself in a thousand ways. It shows more particularly in this way than any other, that a brilliant assistant is likely to be given not less work or let alone because he is getting along fine and getting "A's", but he is likely to be given more work because he is brilliant and because his professor wants to found out the top limit of his capacity and ability, and his professor in Europe is not in the least inclined to give much of his time to the boys that are getting "D's" and "E's". That is not, thank God, that professor's job.

The professor's problem is to add to knowledge and surround himself with an extremely able group of young assistants, and from thereon out he can set his course. But any moral responsibility to a class of, I don't care what size, a class of students, is simply not in the European philosophy.

There is great attention paid to individuality and to originality, perhaps more than with us, and more leeway is given. British students that we had over here in the war, during the war-time, it is not fair to say that they complained, but they certainly were acutely conscious of the fact that they were told what to do next in the medical schools for four years, and were given extremely little leeway to do their own work in their own pace and in their own way.

Now, there is a lack in Europe that is pretty conspicuous, and that is the lack of team-work. It is partly related to this passionate interest in

originality, but I get that lack of teamwork both because I see it over there and because the uniform criticism that we get from foreigners whom we see or whom we bring over to this country on fellowshipp--the uniform point of astonishment for them is how well the Americans work together in scientific teamwork.

That shows, that lack of teamwork shows because aprofessor of physiology feels perfectly infurriated if he has to share the same instrumentation with a professor of pharmacology. You don't do that in Europe. You have your own machine in your own place, and sharing the facilities, I am unhappy to say, including library facilities, is certainly less known and in spots you could say and still be right, that it is unknown.

We have sent lots and lots of shipments of books and I am just sorry to remember how many times when I have asked where the books were, to find that they were stored in the university library and nobody had ever gotten at them, because the European concept of a librarian is a man who guards books, and he does not make them available. He guards them, and he does a damn good job of it.

Now, there is a mixed comment and I bring it under the term of libraries. One of the reasons why the Europeans feel so acutely the losses of the war in the point of medical literature and biological literature is that they are accustomed to reading more languages than we are over here, and far more. I have been to plenty of professors' houses in Scandinavian countries where the four walls of his study, each wall was devoted to a different language, and you see that he means that he has his own library. There is a price tag attached to that.

You can't learn languages competently without a certain investment of time and the pressure on the smaller countries is great. There is pressure on the Dutch and the Danes and the Norwegians and the Swedes and the Finns and the Belgians to master at least one other language than [redacted] really

master it, not to say two more that you have at least the ability to read in it. It is a very impressive thing.

It is also impressive to drift into a child guidance center in Holland, and there are many of them, and out of courtesy to me they held the whole evening in English, and there were about fourteen participants, and they all talked English perfectly easily. I will admit my standards are a little bit catholic and liberal on that, but I could understand them.

I don't know of any psycho-sematic clinic in the US where for the comfort of the visitor the whole stage would be in either Italian or French.

That is why they feel the loss of books so acutely because they have been using other languages much more widely than we do.

I can't help saying in this point of language that there is one great secret that you could allnse if you go abroad. That is to learn to speak English slowly and distinctly because everyone who has a university education can understand you perfectly easily. The charming thing is because they understand, they think that you are damned intelligent, which they didn't think before.

Another item that is perfectly overwhelming at the present time is the poverty You realize that the French for example have gone through an inflation since thethe beginning of the First World War which is of the order of one to 200. We haven't got any article in the US that cost one dollar in 1935, and that now costs $200, and when we do have something like that, or if we do have it, the by-effects, the side effects and the direct effects of that just spread all over the map.

It is the cleaning out of the older people, and I feel like telegraphing if there is a group that can do anything about it, that the most important thing in the field of government it is to stop inflation, because the misery of the older people in Europe because of inflation i[redacted]g that can't be overdrawn.

That inflation shows in a thing which might interest you. In countries where there has been inflation, I would ask what the professor's salary was, the full-time professor, and if they said 8,000, I really wouldn't know whether it was 8,000 a month or 8,000 a year, and furthermore I didn't have any idea what that bought. So I devised this system. I asked 20 people how much it costs for a young man to attend medical school for one year, that is the tuition, which is usually nothing at all, but the books, the clothing and food and housing, and take that total sum which in American would probably be around $1500 in a good many schools, and divide that into the Professor's salary, which might be 6,000, and then you get a quotient of four, and your quotients are good in all countries, and where the quotient is less than 3.5, as it is in many countries in Europe at the present time, then things are going to pieces and they are going to pieces fast because there is no competition for professorial positions.

Where they are four and better, four to seven, it is regular, and it is fairly good, and seven and upwards is excellent, and there are not many places where it is excellent.

This poverty is a peculiar kind of poverty and it hits scientists harder than other people, because so much of the material and instruments, both consumable supplies and instruments in Europe now must be bought in dollars, and dollars are no longer money, they are the money plus the privilege to buy, because it is so damned hard to get dollars, and the same thing goes for South America.

In other words, you can't get dollars. The given exchange rate in the Argentine is a rate at which Americans can buy pesos at the banks, but the Argentines can't buy dollars at that rate and they can't get them at all. So the possession of dollars to purchase scientific ma[redacted]oth money and

the privilege to even make a bid or even to be in the market.

I asked this last time in France and in Switzerland whether there was any work going on in isotopes. There is, they are getting their isotopes from Harwell, both cheaper and quicker than they get them from here, and I simply pass that along as a minor item.

They are awfully unhappy at the discontinuation of the Index Medicos. I had several cases of distress on that. That Index Medico is one of the considerale contributions that this country has made to the whole field of medical scholarship.

Now, there is another thing that is very impressive in Europe at the present time. You ask practically any professor in practically any country what is the main difficulty now, and he will say the number of students. They are overwhelmed with students. In Paris that has accommodations in its physiological laboratory for 80 students at a time, there are 1800 students. And the competition for internship is as bas as that would indicate.

But the tradition is so strong that any student finishing the secondary school can get into the university, that they will take them in and break them in the medical schools rather than go in for any kind of selection. And that, curiously enough, hitches up with the deep, under-ground upper class ruling class feudal tradition of the university being an upper class affair, and since it is upper class there is always certain to be a perfectly enormous burst of criticism if they didn't allow the university to be open.

They say that is where they are completely democratic and they are not going to have the university limited, and the real fact is that they wouldn't be half as tender on that subject if the university weren't already a definitely upper class institution.

They are just as passionately concerned that it [redacted]

classes as anything can be, when they really know it isn't. But it must be kept open, so they keep these things, all of the universities are open to students.

Now, there is only one exception to it and it is a very interesting and curious exception. The Germans have shut down on their admissions to medical schools. They have shut down almost exclusively for the simple reason that the population in Western Germany now contains 12,000 trained German doctors who have come from the Russian occupied Germany, who have slipped over by night and they haven't got a thing that they can do, and they don't see why they should make any more doctors when they have 12,000 doctors.

The Germans have done one rather interesting thing on that limitation. At Frankfort, for example, it is a limitation of one out of seven applicants. That is seven times as many applicants as they would take. They have put a couple of students on the admissions committee, and that is symptomatic of a very curious situation.

The discrepancy between different age groups, decade by decade, in Germany now, is one of such tension and such magnitude that they don't dare shut students out of the medical schools without having some contemporary opinion to help them out, because you see the whole German machinery has been in the 30's raked out of the anti-Nazi's, and then since the war it has been raked this way to rake out all of the Nazi's, and the residium is darned little, and there is a grave amount of tension. That is related to this numerous state of the classes in the German medical schools.

Another correlary of the relationship of the large number of students is this: It is the ratio of teachers to students, and when some of them have said, "Yes, our greatest trouble is the number of students," I have just said, "Just a minute, you mean the ratio of the teaching force to the students?" And they

say "Yes, there are too many students." And I say, "How about having some more teachers?" And they say, "Well, that is against the regulations." And there your tradition comes in with both feet. They can't think of shifting traditions.

That is a traditional set-piece and they have a certain number, and if the students increase, it is too bad for the students, and it doesn't have anything to do with the regulations.

Again, they simply won't believe the student ratios that I told them we had. In Rochester it happens to be two teachers for every student, taking the sum total of all of the teachers at the Rochester Medical School. It is two teachers per student.

Well, it is more like one teacher per 80 students in Paris at the present time, and they are incredulous to put it mildly about our situation. That again is related to a very marked difference that there is and has been for a long time in Europe, namely that the European student has to pay more attention to the art of passing an examination than any of our students have to pay because there are two few teachers to know the quality of the students. You have got to have an examination, and, ergo, the examination becomes extremely important because it is almost the only performance the student has to show the quality of its work.

Now, just two more points. You can often get an idea of a country by what they find extraordinary, or extraordinarily useful or singular as a characteristic or valuable in the US. The Europeans in my experience have been impressed by these fields in the US at the present time—the fact that in the training of our surgeons we are slanting more and more to a physiological training. Second, that they find American anesthetists simply out of the world, something that they don't know at all. And third, they are much impressed by our child guidance and child psychiatry; and fourth, they are [redacted] impressed by the

progress made in America in endochronology and internal secretions, although I am rather surprised that I have had nowhere near as many requests for information this last September and part of August, and I had nowhere near as many requests on the ACTH as I expected there would be. That has not apparently burst on the horizon as yet there.

Now, the two things that they mention the most in terms of the generality of scientific work as I said were teamwork, and this perfectly remarkable thing that you Americans have, namely the equality between the teacher and the student or between the assistant and the teacher and the professor. They stick around pretty much in the atmosphere there still, and the professor does a good deal more authoritative influence than he does here.

Now, there is one other thing and then I will be almost within my limit, and that is the manpower losses in Europe which wouldbe bery hard to exaggerate. They are of two orders. One is the manpower loss that took place in 1914 and 1918, which is showing itself in the group over 50 in Europe, and they are simply minus an enormous number of persons.

Take a fellow like Henry Loshay, the French physiologist, on a sampling basis. I said to him, "What is your experience?" And he said quite simply, "I graduated from the University of Grenob in 1906, and there were seven of us that graduated with honors, and I was the only one that survived the first World War."

Now, it is extremely hard to improve the importance of something that isn't there, because it is hard to prove its absence first of all. It isn't there. But it is a tremendous loss. On topd of that, the French suffered a very heavy loss during 1943 when the Germans took out 280,000 Frenchmen that were making their living particularly in occupied France, and put them in prison camps and only 28,000 have ever been heard of. That is not known where, but it is a forbiddable thing.

The head of higher education there, a fellow named Pierre Shaei, I asked to confirm that story, and he said "Yes, that is substantially true, but you have left out one thing. If the Germans had made that list in 1941 or 1940 and had gotten all of the young French who about that time slipped underground," in other words, if they had had the full choice early in the war and had taken 280,000 and then these were his words, and he was speaking English, "I would not expect France to get to her knees for the next seventy-five years."

You can see the meaning of that. Their potential families are gone, and the tradition of hard work and honesty is gone, and that is the last thing. It is a somber thought to close on, but in the occupied countries for nearly five years the smart thing for young people to do was to cheat the government because the government was the government of a stranger, of a foreigner. And all you can say rather bitterly is that all of the young people learned to be c ooked and now that the government has become their own government they don't yet know the difference and there is a very substantial loss in general public morality and in the absence of the leaders who were removed it is a very difficult situation.

Scientifically I think it is a very spotty picture. The countries that are something like what they used to be are Sweden, Switzerland, and to a certain extent Britain, with qualifications in Britain that you know as well as I do, namely the food difficulty and the shortages all along the line. There are spotty men of brilliance living under great handicaps scattered all over the rest of Europe.

The financial situation and the political situation and the profound uncertainty as to what in the hell is going to happen next sits like a cloud over everybody, and a girl in our office told me in a very intelligent way, a fine girl, 52 years old, so she wasn't a stripling b[redacted] she

said, "Dr. Gregg, if there comes another occupation, I go out of the window. That is one thing that I don't have two of."

And that is very much the atmosphere. It is one in which we not only lead the world in terms of our opportunity, but there are hardly any other entries at the moment, excepting in individual brilliance which is having a darned hard time because of the limitations all along the line.

DR. BRONK: How do you account for the fact, Allen, that England, despite the difficulty it has been laboring under and is still laboring under, is still doing such extraordinary good work in the fundamental aspects of science? Do you think that is momentum and tradition, or what?

DR. GREGG: I think it is partly momentum and I think that they did not have anything like the manpower losses that they had in the first World War, and I think that the English have this thing that I referred to, namely, with limited material, they sit down and say, "Well, if we can't do so many things, the things that we do do we had better select with the greatest care." They have done that, certainly.

DR. BRONK: I was hoping that you would say that, because I think that that has a lesson for us.

DR. GREGG: I certainly do feel it, and you take X-ray crystalography as applied to proteins. The English are right on the ball there and they are having a hard time getting the instrumentality that they want. There are other things that we don't realize, or the majority of us don't realize, and I think it may surprise you to know that 58 percent of the students at Oxford and Cambridge are on fellowships, and they are fellowships accorded very definitely on the basis of student performance.

That is a pretty big fraction. The English are making a change there far greater than we realize in the direction of free education for any boy

that really shows very definite promise. Ours on the whole and roughly speaking is more or less education for everybody.

Some of these things I feel very much as though I were talking about domestic life with my wife present, and Dr. Stern, have you got some qualifications on these generalities?

DR. STERN: I haven't been in Europe for fifteen years or more, but what you say is so similar to what I knew from my own time that I have nothing to qualify it.

These things which are going on in England, should they not very soon change the feudal aspects of British universities?

DR. GREGG: They are changing to a great extent.

DR. STERN: You did not speak about the quality of scientific and medical general work in Europe. I remember during the war, you once gave a speech in which you pointed out how very much important work was being done in Europe, and that we should not overlook this. How is this now?

DR. GREGG: There are two or three things that are very interesting. First of all I actually believe that there is something that one could call the originality of isolation. It is an awfully small number of valid truths that come out that you can discover because you are isolated, but take Monet's operations on the fore-brain. I don't suppose that there is a clinic in the US or in England where somebody would have to, so to speak, in ignorance and isolation, proceeded to scoup out people's fore-brain to the tune that Monet did, but nobody cared. He was completely alone, and nobody knew anything about it, and he comes across something that is of considerable value.

It is the same thing with electric shock therapy coming out of that Italian clinic, where they try everything under heaven, and they try it in a considerable measure of isolation.

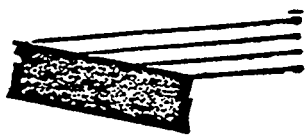
There is also this tremendous emphasis on individuality which has some very interesting advantages. I know I used to think that freedom was just a pleasure principle, but the more I see of this, the surer I am that nature by her many experiments manages to survive because she tries so damn many different ways in genetics combinations, to produce something, and doesn't care if it is different.

The European University reminds me a little bit more of what in this country would be called an Audubon Bird Club. It is a collection of people who are interested and who withdraw from the rest of society and exchange ideas. This is a tremendous exaggeration, but it does result in that.

That is much more the atmosphere of a great many of the universities than it is with us, and out of this tremendous originality or this not necessarily tremendous originality because they are not more original than we are, but under the encouragement given to originality they still produce these things that we shall have to watch pretty carefully.

This is the time to finish the speaking, and thank you all for coming, very much. It has been a pleasure. Tomorrow we meet at 9:30.

(Thereupon, the session adjourned at 5:10 p.m.)



November 28, 1950

Shields Warren, M.D., Director
Division of Biology and Medicine
U. S. Atomic Energy Commission
1901 Constitution Avenue
Washington 25, D. C.

Dear Shields:

Unfortunately, it will not be possible for me to be at the meeting on December 8, but I am passing along some of my ideas in the hope that they will be of some assistance to you and the others present at the conference.

To summarize briefly, in my estimation the biological equivalent of 50 "r" of 1 Mev total body x-radiation will probably provoke an appreciable, but not alarming degree of radiation sickness when given in a single dose. In other words, it would be my estimate, which is somewhat arbitrary as you must realize, that in the range of 25-50 "r" I would not anticipate a serious decrease in operational effectiveness of military or civilian personnel, assuming that they have been suitably indoctrinated and do not develop incapacitating symptoms on a psychological basis. The tendency for radiation sickness to appear would be significantly enhanced if the individuals being exposed had been subjected to previous stresses such as prolonged physical effort, loss of sleep and other types of fatigue. Likewise one might expect some degree of enhancement of the radiation effect if the exposed individuals were subjected to the types of stresses indicated above. The biological equivalents of 150 "r" I expect would be pretty much of an incapacitating dose, but it would seem unlikely that there would be an appreciable number of fatalities, providing the individual did not have some concomitant serious injury from some other source. At the level of 350 "r", I would expect this to be the M.L.D.-50 figure. I should like to introduce an opinion that while my figures might be valid, there will be many operational circumstances in which it will be difficult to predict the exposure that a group of individuals may

The shielding of this 1 Mev radiation was of such a nature that the half-value thickness of the emergent x-rays was 9 mm of copper.

have to undergo to perform a certain manipulation. However, it does seem to me appropriate that both the Atomic Energy Commission and the Armed Forces be given some numbers with a reasonable degree of reliability.

I suspect that one of the reasons that you asked for me to be present was on the question of internal radioactive poisoning which is a field that I have a little more familiarity with than the problem of external irradiation. To summarize briefly, there are three principal routes by which radioactive substances, irrespective of their nature, may gain entry into the body. They are in decreasing significance, inhalation, oral ingestion and entry through abrasions, cuts, etc.

Of these three, inhalation is by far the most important. To indicate the number of millicuries inhaled that might be a crippling or lethal dose, of course, depends upon the radioactive agent, its physical and chemical form, its half-life, nuclear characteristics, etc. There is much that we do not know about this problem, but as a representative figure I would expect that of the order of 10 millicuries of a radio-element such as strontium 89, if inhaled as a soluble aerosol and absorbed would probably be close to the lethal range. This is based on the experience of Dr. Friedell who many years ago gave a patient with widespread metastases from carcinoma of the breast 10 millicuries of strontium 89 by parenteral injection. The patient nearly died and best estimates that one can make would suggest that the bone marrow got of the order of several hundred roentgen. Should the material inhaled be retained in the lung, it works out that the retention of 10 millicuries of a radio-element possessing the nuclear properties of strontium 89 would probably produce a severe and possibly fatal radiation injury to the pulmonary tissue. To the best of our knowledge, the high degree of selective uptake noted in bone for so many radioelements is not observed in lymphoid tissue notably spleen, unless the substance is administered in colloidal form. Likewise the gonads do not, to the best of my knowledge, show any unusual behavior towards fission products or materials that might be made radioactive on a large scale, such as tantalum. Ablation of the thyroid requires about 50 millicuries of I^{131} and this is not a likely hazard without much larger activities from other fission products being present.

As you will probably gather from the above comments, I have been speaking of immediate effects in the sense of disabling changes that might take place in the range from a few hours to a couple of months. Long-term effects such as genetic changes, neutron induced cataracts, and carcinogenesis are a little more difficult to assess, and frankly under the present state of affairs, I feel that more concern should be given to the acute rather than the chronic effect.

It seems to me that it is very desirable to determine in man the range of total body radiation required to induce an appreciable decrease

Shields Warren, M.D. November 28, 1950

in his capacity to execute intricate tasks for which physical well being is essential. If this be done, it should in my estimation be not only total body radiation, but from gamma rays in the 1 to 2 Mev. energy level. For both politic and scientific reasons, I think it would be advantageous to secure what data can be obtained by using large monkeys such as chimpanzees which are somewhat more responsive than the lower mammals. Scientifically, the use of such animals bears the disadvantage of the fact that they are considerably smaller than most adult humans and a critical evaluation of their subjective symptoms is infinitely more difficult. If this is to be done in humans I feel that those concerned in the Atomic Energy Commission would be subject to considerable criticism, as admittedly this would have a little of the Buchenwald touch. The volunteers should be on a freer basis than inmates of a prison. At this point, I haven't any very constructive ideas as to where one would turn for such volunteers should this plan be put into execution. There is much to recommend the use of adult males past the age of 50 in good physical status. However, one can't be certain that these people would respond in a similar manner to the 20 to 40 age group. In concluding, the picture as I see it is to ascertain what is the disabling range and factors which might influence it.

I trust that these comments may have been of some assistance to you, and again, I want to express my regret at not being able to be on hand for the meeting.

With very best regards.

Sincerely yours,

Joseph G. Hamilton, M.D.

JGH:bs

Copy 1 of 2/A - Shields Warren, M.D.
2 of 2/A - J. G. Hamilton - files

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MINUTES

of the

PROGRAM COMMITTEE

Division of Biological and Medical Research
Argonne National Laboratory

* * *

The eleventh meeting of the Program Committee began at 10:15 A.M. on January 12, 1951, at Site B.

Present:

A. H. Brues, Chairman
R. J. Hasterlik
L. D. Marinelli
F. C. McLean
J. E. Rose
R. E. Zirkle
E. L. Powers, Executive Secretary

R. L. Cardwell

J. S. Schubert (part time)

* * *

Reorganization of Research in Biology, Medicine and Radiological Physics
(See Minutes of 10/6/50, p. 4-23; and 1/5/51, p. 10-74)

Dr. Brues noted that Dr. Schubert was invited to this meeting in order to discuss with the members of the Program Committee the relationship of himself and his group to the research activities of the Division of Biological and Medical Research and to the service activities of the Health Services Division. For Dr. Schubert's benefit, Dr. Brues reviewed briefly the scope of the reorganization plans as discussed in the last meeting. He recalled the general opinion that the Schubert group belonged programmatically and administratively within the Division of Biological and Medical Research, but that some responsibilities toward the bioassay functions of the Health Services Division should be maintained by the group. In regard to Dr. Lawrence S. Myers, Dr. Schubert said that he felt Dr. Myers could not be satisfied with an entirely routine job, but that Myers would have more time in the future to develop analytical methods which are needed for fecal analyses. The development of these analytical methods and the assistance

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Myers would give to investigators in H^3 analyses and to investigators dealing with low levels of C^{14} would constitute an amount of research work acceptable to Myers while allowing sufficient time for the routine aspects of the bioassay services. Accordingly, Schubert agreed that Myers could be listed formally as devoting about 90 per cent of his time to bioassay and about 10 per cent to research. He agreed that it would continue to be necessary for him to have frequent contact with Myers and that he probably would be the best liaison between bioassay services and the Program Committee. In order to formally recognize this relationship, it was agreed that Dr. Schubert would be listed as devoting approximately 10 per cent of his time to distributed services, being responsible to Dr. Hasterlik as Director of Health Services for this portion of his time, and that the remainder of his time would be spent under the authority of the Division of Biological and Medical Research. Dr. Schubert left the meeting at this time.

There were several questions raised concerning the names of research groups and several suggestions were incorporated into the new listing.

Dr. McLean said that with the death of the Noyes Panel, there is no laboratory group within the AEC which now recognizes formally the need for thought on military and civilian defense problems. While he does not feel that a special group carrying such a name need be set up, it should be agreed that one of the responsibilities of some group (e.g., Special Problems) would be this type of problem.

Human Radium Studies
(See Minutes of 11/17/50, p. 8-59)

There was brief discussion concerning certain legal aspects of the current study of toxicity of Ra in humans. One of the questions being considered by the Legal Department of ANL is the acquisition of bodies of persons known to have ingested Ra. It appears that a Superior Court order for exhumation with the consent of the nearest relatives is all that is necessary to obtain the bodies. If there is no kin, a Supreme Court order is needed. Dr. McLean pointed out that a person, when placed in a museum, is considered by the courts to be legally buried. Dr. Hasterlik could foresee no serious problems in obtaining authority to exhume the bodies of the people of interest to the Ra group.

Dr. Hasterlik said that one of the Ra patients, Mrs. K., is becoming quite ill and it is likely that she will die in the near future. This patient is of particular interest because external γ ray measurements indicate a total Ra content of 2 μg. The usual experience has been that necrotic symptoms are not demonstrated by persons containing less than 1 μg. For this reason, all other possible diagnoses must be carefully ruled out, and to this end a biopsy on her foot is planned for next week.

Arnold, who has had no military experience, has requested of his Board a deferment to July 1, 1951, which marks the end of his term as Fellow. He is investigating autoradiographic means of locating ...ers deposited in bone, a subject of considerable interest to the ...n at the present time in view of its concern with chronic effects ...y radioactive elements.

Dr. Brues expressed the opinion that a move to retain Dr. Arnold in ... field in which he has been working for a year and a half and for ... he has shown some aptitude should be considered.

Dr. McLean said that it was his experience that Draft Broads should ... dealt with by persons other than the individual and that the Army ... be dealt with after a person has enlisted. He felt that the Army ...ities show much more sympathy for an appeal for the efficient ...tion of a scientist or physician than the ordinary Draft Board is ... to. Mr. Marinelli recalled General Cooney's appeal for referrals ...minutes of 10/6/50, p. 4-21) and suggested that should all else fail, ...old be recommended to him.

Dr. Looney, who is responsible for a large part of the administra- ... the current studies on the metabolism and toxicity of Ra in ...eings, is in the Organized Reserves of the U. S. Navy. Up to ... his Commanding Officer has shown a willingness to cooperate and has ...d him to remain with Argonne. Dr. Brues felt that a continuance ... type of deferment should not be expected and wondered if a more ... policy emanating from a higher level is not in order. He expressed ... belief that the administration of the Laboratory is not anxious to ... the initiative in asking for assignment of military personnel on ...l duty here at the Laboratory. Dr. Brues said he would attempt to ...ver the mind of the Committee on Medical Sciences of the Panel on ...al Aspects of Atomic Warfare, National Military Establishment, ...rning persons like Dr. Looney.

Concerning draft deferments in general, it was agreed that it would ...ry wise for the Laboratory to have a paragraph on file for each man ...ting a request for deferment, describing the particular way in ... he is contributing to the research of the Laboratory.

Argonne Cancer Hospital

Dr. Hasterlik discussed briefly the research program of the Argonne ...r Hospital. It is his understanding that the Argonne Laboratory is ...ed to assist in the determination of the research program to be ...d out in this installation, and he requested members of the Program ...tee to consider the kinds of problems that are properly and most ...iently investigated in it.. The program is to be discussed with ...geshall, Director of the Argonne Cancer Hospital and Dean of the

vision of Biological Sciences, in the very near future, and Dr. Hasterlik shed to have some definite proposals ready for consideration. As parts a general discussion concerning the program, it was pointed out that e current investigation of toxicity of Ra in human beings is an excelnt example of the kind of activity for which a hospital is needed and use for which the Argonne Cancer Hospital is intended. The Argonne ncer Hospital can reasonably be expected to provide the access to linical material needed by the Division in its cancer investigations and rtainly the hospital is the proper place for experiments involving dioactivity in human beings.

Concerning the last subject, Mr. Marinelli asked if there is a neral policy concerning human experimentation. Dr. McLean said that e Advisory Committee of the Division of Biology and Medicine of the AEC s been approached several times in the past for a general policy and s refused to formulate one. Apparently, proposals for human experiits with radioactivity will continue to be judged on an individual basis.

Toxicity Laboratory

to the present time, the Toxicity Laboratory has been supported the Division of Military Applications through the Division of Biology Medicine of the Commission. Dr. McLean felt that further support on s basis will be difficult and that it is not likely the present conct which expires October 1, 1951, will be renewed. There are no ications as to what will happen to the facilities nor to the persons loyed by the Laboratory after expiration of the present contract. McLean listed several possibilities — 1.) It may return to the ical Corps as the type of laboratory it was during the last war, 2.) may retain an interest in radiation biology but be supported by one the Services. For example, the Air Force which has a considerable rest in the deleterious effects of radiation, their prevention and py, has no facilities of its own and it may be interested in acing one, 3.) The Toxicity Laboratory may continue to be occupied military and civilian defense and atomic warfare as an independent ract, or as a part of the Argonne National Laboratory.

It is Dr. McLean's impression that a proposal to incorporate the city Laboratory into Argonne Laboratory would not be unwelcome in in quarters and that the facilities and certain of the personnel may ed on problems relating to civilian and military defense (see es of 1/12/51, p. 11-80). Dr. Powers said that he doubted that the nistration of the Laboratory would feel kindly toward assuming reility for the physical plant on the campus occupied by the Toxicity ory because of the Laboratory's current heroic effort to consolioographically.

.e of CP-3, the number which just makes possible lethal exposures
; in reasonable lengths of time. Drs. Zirkle and Vogel are to
:h Dr. McCorkle to settle design questions and it is likely that
source will finally become available to the Division.

Human Toxicity Tests

Jack Schubert's desire for a test in humans of the toxicity of
:carboxylic acid was discussed. The compound shows some promise
as a remover of deposited Be. Obviously the Laboratory should not
irectly involved in this sort of testing program, and it is sug-
hat perhaps some pharmaceutical house could be persuaded to handle
similar tests. The Chairman said he would inquire of the Medical
f the Division of Biology and Medicine, Atomic Energy Commission,
ce.

Human Radium Problem

a patient referred to previously (see Minutes of 1/12/51,
articular interest because the low estimated radium content
ical symptoms of radium poisoning demonstrated by her, underwent a
last week. Definite diagnosis of fibrosarcoma has been made. A
of the biopsy material has been sent to Dr. Robley D. Evans for
Ra^{228} determinations. Dr. Hasterlik also reported sending to the New
erations Office information from the Barker files concerning certain
lyses which the U. S. Radium Corporation had made at one time.

e other item was reported for the information of the Committee. The
who was interested in running a newspaper story of the toxicity
as been consulted. This individual is an employee of the State
Department and his motive in this instance was to demonstrate how
institutions are cooperating in scientific research. When the delicate
of this particular research was explained to him, he agreed not to
his publicity until such time as Dr. Hasterlik thinks it proper.

Mesothorium

orrespondence between W. P. Norris and H. Deplanche of The Rare
s and Metals Company, Inc., 21 East 40th Street, New York 16, New
esulted in their offering the Laboratory 8 to 10 mg Ra^{228} (see
s of 1/12/51, p. 11-81). If the Laboratory were willing to divide
nto lots of 8 to 10 mgs, the Minerals Company would waive
the Ra^{228}. Otherwise the only Ra^{228} (mesothorium bromide)
le from them at the present time is a tube of Ra^{228} No. T 162, which
led on April 22, 1944 and measured last on February 17, 1950, as
ing 69.1 mg Ra equivalent. The cost is $35.00 per mg ex-warehouse,

...d by Mr. Wahl, namely 50 μc per cubic meter of air as T_2 or HT, is the ...m permissible level recommended by the International Commission on ...ological Protection (see Nucleonics, February 1951, pp. 70-74). Mr. ... pointed out that this figure differs somewhat from that used by this ...atory at the present time as the mpl for operations. Allowing ...week total dosage, 23 $\mu c/m^3$ is indicated. Since an allowance for ... to other radiations must be made, 10% of this figure, or 2 $\mu c/m^3$ ..., is the mpl for Argonne operations. The need for experiments on ...er and metabolism was briefly discussed.

Human Radium Studies

...r. McLean told of the recently initiated conferences with various ...ted members of the division concerning the decontamination of persons ...ing radium. This group will continue as one of the study groups pre... described (see Minutes of 10/20/50, Appendix I, pg. 5-28). Dr. ...ik reported that his recent examination of the files of the U. S. ...orporation reveals the disturbing information that beginning in ... there was rather free substitution of RdTh (Th^{228}, $T_{1/2}$ = 1.9 years) ... (Ra^{228}) in the paints used for clock dials. The Th^{228} contents ... from 2 to 25% of the total activity, indicating great difficulty in ...ing the original activity in a particular patient. Furthermore, it ... necessary now to appreciate Th^{228} toxicity in addition to that of ... Ra^{226}. It seems likely that the dial painters will not constitute ...urce of information concerning Ra toxicity in humans.

Consultants

... ...es announced the intention of the Division to contract with ... Ward Wainwright as a consultant. Dr. Wainwright was formerly ...es. He is interested in radioautography and will assist and ... Division in this field.

* * *

...ing adjourned at 11:30 A.M.

* * *

E. L. Powers
Executive Secretary

"MEMO ROUTE SLIP Form AEC-98 (Rev. May 14, 1947)	See me about this. / Note and return.	For concurre / For signatu	For action. / For information.
O (Name and unit) Dr Shields Warren attn. H. Brown	INITIALS DATE	REMARKS For your consideration and reply.	
O (Name and unit) Dr. Warren	INITIALS DATE	REMARKS T Franks J Martens	
O (Name and unit)	INITIALS DATE	REMARKS Believe this to be a matter warranting your personal attention.	
ROM (Name and unit) J Martens Rm 13		REMARKS AEC 1-30-51	
IONE NO.	DATE 1-29.		

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DOE ARCHIVES

Los Alamos, New Mexico
January 22, 1951

Dr. Alberto F. Thompson, Chief
Technical Information Service
U. S. Atomic Energy Commission
1901 Constitution Avenue, N.W.
Washington 25, D.C.

Dear Dr. Thompson:

I find myself concerned in the course of duty with the review of papers relating to human experimentation.

It has been suggested by various persons here that there exist regulations or policies of the AEC on this subject, e.g., a paper by a committee in Biology and Medicine, but I can find no definite information beyond the idea that these regulations are comparable to those of the American Medical Association: that an experiment must be performed under the supervision of an M.D., with the permission of the patient, and for the purpose of seeking a cure.

For my personal information, can you tell me whether there is any definite AEC policy on this subject, and what the policy is? Are there any staff papers available?

Yours very truly,

Les

Leslie M. Redman

Re Redman request:—

Perhaps Dr. Donahue could assemble + forward data based on

(1) Med. Bd. of Review ... pp. 11 — Sec. VI, 1st ¶

2) "The secrecy with which some of the work of the AEC has to be conducted creates special conditions for the clinical aspects of its work in that the public is aware of the necessity for secrecy and of the subsequent difficulty of probing into it." Gregg — Sept U.S.

3) Doc. 2404 — quote 2nd TP from C.6 (We believe . . .) to end of TP.

With these data, consider also supervision by M.D., not self-experimentation ... another M.D. to supervise.

DOE ARCHIVES

0015327

CONFIDENTIAL

March 5, 1951

Mr. Leslie M. Redman
"D" Division
Los Alamos National Laboratory
Atomic Energy Commission
Los Alamos, New Mexico

Dear Mr. Redman:

Dr. Alberto F. Thompson, Chief, Technical Information Service, has asked me to reply to your letter of January 22, 1951, concerning policies on human experimentation. The following statements have guided the Division of Biology and Medicine in its attitude towards this problem:

First, in a letter from Carroll Wilson, General Manager, to Dr. Robert Stone, University of California, dated November 5, 1947, appears the following from a statement prepared for the Commissioners by the Advisory Committee for Biology and Medicine:

> "We therefore wish to record our approval of the position taken by the medical staff of the AEC in point of their studies of the substances dangerous to human life. We believe that no substances known to be, or suspected of being, poisonous or harmful should be given to human beings unless all of the following conditions be fully met: (a) that a reasonable hope exists that the administration of such a substance will improve the condition of the patient, (b) that the patient give his complete and informed consent in writing; and (c) that the responsible nearest of kin give in writing a similarly complete and informed consent, revocable at any time during the course of such treatment."

Secondly, the Report of the Medical Board of Review dated June 20, 1947, on page 11, Section VI, first paragraph states:

"Secrecy in scientific research is distasteful and in the long run is contrary to the best interests of scientific progress. The Board of Review recommends that insofar as it is compatible with national security, secrecy in the field of biological and medical research be avoided."

Thirdly, Dr. Alan Gregg, Chairman of the Advisory Committee for the Division of Biology and Medicine stated at the September 1948 meeting of the Committee:

"The secrecy with which some of the work of the Atomic Energy Commission has to be conducted creates special conditions for the clinical aspects of its work in that the public is aware of this necessity for secrecy and of the subsequent difficulty of probing into it."

With these basic ideas in mind as guiding principles, I would like also to urge upon you the importance of having any experimental work which involves human beings supervised by an M.D. This holds equally well for self-experimentation by scientists whether or not they are physicians. If in the latter category, any such self-experimentation should be done only under the supervision of another physician.

Sincerely yours,

Shields Warren, M.D.
Director
Division of Biology and Medicine

DUNHAM:mar

OFFICE ▶						
NAME ▶						

DATE: 18 September 51

FROM : Code [redacted]

SUBJECT: Proposed Means of Proper Authorization and Safegu ard in Use of Radio-Isotopes.

Encl: (1) Copy of PERMISSION TO USE RADIO-ISOTOPES
(2) Copy of AUTHORIZATION BY THE ISOTOPE COMMITTEE" FOR THE USE OF A RADIO-ISOTOPE

1. Enclosures (1) and (2) forwarded for comments as to legal value.

W.E.Wiemend
D.E.DEMENT

7212 — X 63656 Plant
Referred to Radioactive Briefing X 63020 AE Tipton File A16-3/NN
Assistant for Safety 3 = 03

COPIED: 7/6/94
RECORD GROUP: #52
ENTRY: #15C
FILE: A16-3/DD
1951

ISOTOPE

Date:

1. It is the request of this patient _____ that (he-she) be given a (tracer-therapeutic) dose of _____ by the staff of the Radioisotope Laboratory. This laboratory is supervised by the Hospital Board for the Control of Radioisotopes in Human Patients.

2. The patient understands that all redioisotopes used in this hospital are obtained from the Atomic Energy Commission for research projects.

3. The method of administration and general plan of study have been approved by the Medical Committee of the Atomic Energy Commission and the local Committee for the Use of Radioisotopes in Human Patients.

4. It is to be understood that the U. S. Navy, the Naval Hospital at Bethesda, Maryland, its agents and its personnel assume no responsibility for the results or effects of this study nor of its interpretation.

(Signed) _____

(Signed) _____

(Witness) _____

(Witness) _____

1. This study determines the ability of the thyroid to concentrate iodine. The amount and distribution of the radioiodine is measured by means of Geiger-Muller counters on the skin over the thyroid gland. The amount of radioiodine excreted in the urine is measured in specimens saved over a period of 48 hours.

2. The referring doctor should discuss with the Radioisotope Laboratory [illegible] recent use of the following:

(a) Thyroxine, propylthiouracil, or any type of hormone therapy

(b) Iodine containing preparations:

(1) Lugol's solution or syrup of Hydriotic acid.
(2) Diodrast (I.V. and retrograde pyelograms, arteriograms, [illegible] of sinus tracts).
(3) Lipiodol (Bronchograms, injection of sinus tracts).
(4) Pantopaque (Myelograms).
(5) Priodax (Gall Bladder series)
(6) KI (Expectorant cough medicines, e.g. Brown's Mixture).
(7) Argyrol (Bladder and urethral infections)
(8) Thiocyanates (Hypertension therapy)
(9) Thimerin (Mercurial Diuretic)
(10) Diodoquin and Chiniofon (antimalarials).
(11) Diiodofluorescein (Brain tumor studies).
(12) Vioform (Skin ointment)
(13) Tincture of iodine (Skin antiseptic)

3. Restrict the following foods as much as possible for [illegible] and [illegible] hours following the study: iodized salt [illegible] liver, nuts (peanuts and walnuts), [illegible], turnips, [illegible] peaches and pears.

4. Avoid all enemas and use of laxatives to this patient [illegible] hours preceding and the first 24 hours of the study. Please [illegible] ient has loose or frequent stools, as it requires us to make [illegible] the stools for possible radioiodine elimination by this route.

5. Urine Collections:

Save all urine from the time of the dose on for 48 hours [illegible] as listed below. Save in accordance with the labels on the [illegible] furnished. Use only the containers furnished by this laboratory.

Collection schedule will be:

12 hour specimen
24 hour specimen
48 hour specimen.

6. If there are any questions, call the Radioisotope Laboratory [illegible]

7. Time of dose ______________________

No food or drink after ______________________
hour day month

Please insert this page as part of the Patient's chart.

____
Head, Radioisotope [illegible]

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1951

Name: _____ Hospital Admission No. _____

Autopsy No. _____

Isotope Administration:

Isotope	Treatment or Tracer	Dose	Date Administered

Results of Radiac Survey:

Highest measurement external skin surface _____

Highest measurement inside body cavity;

With viscera intact _____

With viscera removed _____

Highest measurement external skin surface after viscera removed _____

Remarks: _____

This certifies that the remains of _____
have been examined by Radiac Survey and is below the accepted tolerance dose-rate of 6 mr/hour. There will be no health hazard involved by the mortician performing the embalming provided he wears rubber gloves.

_____
Radiac Survey Officer

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ENTRY: #15C
FILE: A16-3/DD
1951

[redacted] TRACER CASE #_____

RADIOISOTOPE LABORATORY REPORT

_____TRACER STUDY #_____

Patient's Name_____ ___ ___ ___
Last First Initial Age Weight Height

_____ _____ _____
Date of Request Rank or Rate Ward or Out-Patient

_____
Provisional Diagnosis

Reason for Tracer Study:

_____
Doctor Requesting

_____

_____
Head, Radioisotope Laboratory

_____
Chief of Radiology

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RECORD GROUP: #52
ENTRY: #15C
FILE: A16-3/DD
1951

[redacted], MARYLAND THERAPY CASE #_____

RADIOISOTOPE LABORATORY REPORT

_____ THERAPY #_____

Patient's Name_____ ____ ____ ____
Last First Initial Age Weight Height

_____ _____ _____
Date of Request Rank or Rate Ward or Out-Patient

_____
Provisional Diagnosis

Rationale for Radioisotope Therapy:

_____
Doctor Requesting

_____

Radiation Tissue Dose

Estimated Tumor Dose:
Estimated Skeletal Dose:
Estimated Total Body Dose:

_____
Head, Radioisotope Laboratory

_____
Chief of Radiology

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RECORD GROUP: #52
ENTRY: #15C
FILE: A16-3/DD
1951

Date received	
Date made	
Signature	

Department of the Navy
Bureau of Medicine and Surgery
Washington 25, D. C.
26 September 1951

MANUAL OF THE MEDICAL DEPARTMENT

ADVANCE CHANGE 1-3

The changes listed herein are effective upon receipt. Insert this change in front of the Manual of the Medical Department, and mark "1-3" opposite the below listed articles and subarticles in the Manual text. The symbol "1-3" indicates that this is the third advance change issued in advance of printed change 1.

H. E. Pugh
H. E. PUGH
Chief, Bureau of Medicine and Surgery

Summary of Articles and Subarticles Affected

1-13 through 1-19	5-10	16-7(1)	22-21(3)(a)	23-106(1)
3-36	16-3(1)	16-21	23-2 (MONTHLY, MED-08)	

1-13 through 1-19 New articles

Section IV. RESEARCH

1-13. Statement of Policy

(1) The fundamental policy of the Bureau is to encourage and support research and development in medical, dental, and allied sciences directed toward the solution of problems affecting the health, safety, selection, and efficiency of the personnel of the Department of the Navy and other branches of the Department of Defense.

(2) The direction of the research activities of the Medical Department of the Navy shall be centralized in the Research Division of the Bureau.

(3) Development, testing, and evaluation shall be the responsibility of the Bureau Coordinator for Research and Development (art. 1-12(25)).

(4) There shall be no fixed apportionment of basic research and applied or developmental research.

1-14. Scope

(1) The fields of research studies in medicine, dentistry, and allied sciences shall include the broadest aspects of medical and dental problems related to submarine, shipboard, aviation, amphibious, and field activities, sea transport, and military personnel.

(2) Research and development shall be concerned primarily with pertinent operational requirements of the Navy as promulgated by the Chief of Naval Operations. A continuous program of research in the basic sciences that affect military medicine and dentistry, and their ancillary branches, shall be maintained. In time of war and national emergency, the major effort and attention shall be directed to the practical application of improved methods of medical and dental defenses against the weapons, health hazards, and agents of modern warfare.

(3) Naval hospitals and other naval medical activities are encouraged to conduct clinical research, including studies of diseases and injuries, statistical records of series of cases, appropriate therapeutic trials, and other phases of clinical investigation. The research projects and the therapeutic trials must be authorized by and reported to the Bureau of Medicine and Surgery, through its

Research Division. Application may be made on form NAVMED-98 or on other official forms that may be provided for this purpose.

1-15. Laboratories and Facilities

(1) In addition to the naval installations, in hospitals, infirmaries and dispensaries, and in the medical and dental facilities of ships and stations, the Bureau will maintain research laboratories and facilities separately and in cooperation with other bureaus, the Office of Naval Research, and the Marine Corps.

1-16. Projects

(1) In general, projects will be selected by individual investigators who shall submit their proposals, via official channels, to the Bureau for consideration for approval. However, the Bureau may assign projects to any of the various facilities, when strategic or tactical problems presented by any of the bureaus of the Navy so warrant. Cooperation with other services may be effectuated by individual investigators upon the Bureau's approval or direction.

(2) The selection and approval of projects will depend on the desires, initiative, and competence of the research workers; the available facilities; and the special opportunities offered by the location and environment of particular establishments. In the conduct of their studies, investigators will be given the greatest possible freedom consistent with naval policies and the security regulations as administered by their commanding officers. Investigators will be encouraged to arrange through the Bureau for consultation with civilian scientists, for collaboration with civilian institutions of learning and research, and for interservice cooperation. The Bureau will cooperate in facilitating the exchange of information, the authorization of contract research through the Office of Naval Research, and provision of medical and dental intelligence to proper authorities, via official channels, and will maintain liaison with research activities in foreign countries.

(3) At command research units and/or laboratories under the Bureau's management control, pilot studies may be undertaken at the discretion of the commanding officer, who shall be responsible for the conduct of such studies and reporting of same to the Chief of the Bureau of Medicine and Surgery.

1-17. Experimentation on Personnel

(1) Experimental studies of a medical nature involving persons in the Naval Establishment are forbidden except when the experimental design in each case has received the prior approval of the Secretary of the Navy. All such requests shall be forwarded via the Bureau for consideration and recommendation to the Secretary of the Navy. In the case of military personnel or their legal dependents, recommendations or requests received shall be made by the Bureau and forwarded to the Chief of Naval Personnel, the Commandant of the Marine Corps, or the Commandant of the Coast Guard, as appropriate, prior to submission to the Secretary of the Navy.

(2) Participation by personnel of the Naval Establishment (military and civilian) shall be on a voluntary basis only. Volunteers will not be required to execute a release from future liability for negligence attributable to the Navy. Such studies shall in no way interfere with the training or other performance of normal duties of the personnel involved.

(3) For each instance a statement shall be entered into the individual's Health Record indicating the project number and the physical and psychological effect, or lack of same, resulting from the investigation. In case of civilian volunteers, the commanding officer shall cause a similar entry to be recorded in the individual's personnel file.

1-18. Trials of Commercial Items, Specialties, and Pharmaceutical Products

(1) Authority to conduct clinical, laboratory, or field trials at naval medical activities of drugs, materials, or devices presented by commercial firms may be granted by the Bureau of Medicine and Surgery, if facilities are available and provided that such trials will sufficiently contribute to naval operations to warrant approval. Requests for Bureau review, coordination, and approval of such trials shall be made on form NAVMED-98 or on other official forms that may be provided for this purpose. Reports shall be marked "For Official Use Only" and shall be submitted to the Bureau. All such reports become the property of the Bureau which assumes no obligation to or for any commercial firm. Commanding officers shall take appropriate steps to prevent the unauthorized release of information on trials which might be utilized for advertising purposes to promote sales of commercial products.

1-19. Technical Reports and Public Releases

(1) The Bureau of Medicine and Surgery requires interim and final reports on all projects or subtasks conducted under a project. Interim reports shall be submitted semiannually, as of 30 June and 31 December and at such other times as significant phases

26 SEP 51

APPENDIX 7

MANUAL OF THE MEDICAL DEPARTMENT

Manual of the Medical Department, 26 September 1951, Section IV, Research Articles 1-13 through 1-19 are reproduced below:

1-17. Experimentation on Personnel

(1) Experimental studies of a medical nature involving persons in the Naval Establishment are forbidden except when the experimental design in each case has received the prior approval of the Secretary of the Navy. All such requests shall be forwarded via the Bureau for consideration and recommendation to the Secretary of the Navy. In the case of military personnel or their legal dependents, recommendations on requests received shall be made by the Bureau and forwarded to the Chief of Naval Personnel, the Commandant of the Marine Corps, or the Commandant of the Coast Guard, as appropriate, prior to submission to the Secretary of the Navy.

(2) Participation by personnel of the Naval Establishment (military and civilian) shall be on a voluntary basis only. Volunteers will not be required to execute a release from future liability for negligence attributable to the Navy. Such studies shall in no way interfere with the training or other performance of normal duties of the personnel involved.

(3) For each instance a statement shall be entered into the individual's Health Record indicating the project number and the physical and psychological effect, or lack of same, resulting from the investigation. In case of civilian volunteers, the commanding officer shall cause a similar entry to be recorded in the individual's personnel file.

22 Apr 63

... of laboratory employment in an effort to ... a creative atmosphere and conditions conducive to conscientious scientific productivity. ... development programs shall be effected and ... professional-grade personnel shall be encouraged to participate in the activities of professional societies.

1-8. Scope

(1) The fields of research studies in medicine, dentistry, nursing, and allied sciences shall include the broadest aspects of medical, dental, and nursing problems related to submarine, shipboard, aviation, amphibious, and field activities, sea transport, and military personnel.

(2) Research, development, testing, and evaluation shall be concerned principally with pertinent Naval Research Requirements as promulgated by the Chief of Naval Research. A continuous program of research in the basic sciences that affect military medicine, dentistry, and nursing, and their ancillary branches, shall be maintained. In time of war and national emergency, the major effort and attention shall be directed to the practical application of improved methods of medical and dental defense against the weapons, health hazards, and agents of modern warfare.

... Naval hospitals and other naval medical activities are encouraged to conduct clinical research, including studies of diseases and injuries, statistical records of series of cases, appropriate therapeutic trials, and other phases of clinical investigation. The research projects and the therapeutic trials ... be authorized by and reported to BUMED through its Research Division. Application may be made on form NAVMED-1436 or on other official forms that may be provided for this purpose.

1-9. Laboratories and Facilities

(1) In addition to the usual installations, in hospitals and dispensaries, and in the medical and dental facilities of ships and stations, BUMED will maintain research laboratories and facilities separately and in cooperation with other bureaus, the Office of Naval Research, and the Marine Corps.

1-10. Projects 13-43(1) 6500.2

(1) Projects for research will be established by BUMED in accordance with Naval Research Requirements as promulgated by the Chief of Naval Research. Tasks under the project will be assigned to research activities by BUMED or at the request of the activity. Proposals for research will be submitted by individual investigators via official channels for consideration and technical approval. Cooperation with other services may be effectuated by individual investigators upon BUMED approval or direction.

(2) The selection and approval of research proposals will depend on the desires, initiative, and competence of the research workers; the available facilities; and the special opportunities offered by the location and environment of particular establishments. In the conduct of their studies, investigators will be given the greatest possible freedom consistent with naval policies and the security regulations as administered by their commanding officers. Investigators will be encouraged to arrange through BUMED for consultation with civilian scientists, for collaboration with civilian institutions of learning and research, and for interservice cooperation. BUMED will cooperate in facilitating the exchange of information, the authorization of contract research through the Office of Naval Research, and provision of medical and dental information to proper authorities, via official channels, and will maintain liaison with research activities in foreign countries.

(3) At command research units and/or laboratories under BUMED management control, pilot studies may be undertaken at the discretion of the commanding officer, who shall be responsible for conducting such studies and reporting them to the Chief, BUMED.

6710.49 -6-134E ... 6470.7, 6710.49A

1-11. Experimentation on Personnel

(1) Experimental studies of a medical nature involving persons in the Naval Establishment are forbidden except when the experimental design in each case has received the prior approval of the Secretary of the Navy. All such requests shall be forwarded via BUMED for consideration and recommendation to the Secretary of the Navy. In the case of military personnel or their legal dependents, recommendations on requests received shall be made by BUMED and forwarded to the Chief of Naval Personnel, the Commandant of the Marine Corps, or the Commandant of the Coast Guard, as appropriate, prior to submission to the Secretary of the Navy.

(2) Participation by personnel of the Naval Establishment (military and civilian) shall be on a voluntary basis only. Volunteers will not be required to execute a release from future liability for negligence attributable to the Navy. Such studies shall in no way interfere with the training or other performance of normal duties of the personnel involved.

(3) For each instance a statement shall be entered in the individual's Health Record indicating the project number and the physical and psychological effect, or lack of same, resulting from the investigation. In case of civilian volunteers, the commanding officer shall cause a similar entry to be recorded in the individual's personnel file.

IN CH 3 ... page 1-7 WILL ... START IF SEC III PATCH 36

Loren B. Poush, Code 11, USN, to Code 74, USN (Bureau of Medicine and Surgery) 18 October 1951 ("Legal comments relative to proposed means of proper authorization and safeguard in use of radioisotopes") (ACHRE No. NARA-070794-A-4).

[redacted]

18 Oct 1951

NARA-070794-A

[redacted]

From: Code 11
To: Code 74

Subj: Legal comments relative to proposed means of proper authorization and safeguard in use of Radioisotopes

Ref: (a) Code 74 memo of 18 Sep 1951 to Code 11

1. Enclosure (1) of reference (a) consisted of a blank form which when executed by a patient or responsible next of kin would permit admission of radioisotope medical diagnosis or treatment. Enclosure (2) consists of a form which when executed by the "Isotope Committee" for the use of a radioisotope in the case of a specifically named patient would authorize and direct the staff of the radioisotope laboratory to administer the approved dosage.

2. Attached also to the file where some forms collateral to application for authorization of use of radioisotopes.

3. Previous informal discussion by Code 11 on this subject indicated that some concern exists in the Bureau with respect to the liability of the individual medical officer and to the liability of the Government for other than contemplated results in this category of diagnosis and treatment. Any such liability depends upon whether or not the responsible medical officer devoted appropriate care under the circumstances. In other words, if proper care be devoted to the treatment and the treatment be at the same time reasonably accepted by specialists in the field, no liability arises. The acceptance of this treatment by specialists in the field would be demonstrated presumably by action of the Isotope Committee executed on a form similar to Enclosure (2). In the event that Code 74 did not consider the Isotope Committee to represent specialists in the field, it is felt that perhaps the form does not indicate the qualifications of the Isotope Committee to the extent that may be possible. However, only specialists may determine that.

4. The legal effect of Enclosure (1) may be considered in two senses. In the first sense a statement by the patient that the hospital and the doctors concerned are absolved of responsibility (liability) for results or effects of "study" or of "interpretation" and "release from responsibility resulting from unforeseen effects" is subject to the legal principle:

> One cannot provide by contract against liability for negligence and this principle applies to every species and degree or negligence or tort.

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ENTRY: #15C
FILE: A16-3/PD
1951

Subj: Legal comments relative to proposed means of proper authorization and safeguard in use of Radioisotopes

5. The Bureau, therefore, should assume that should negligence be established, the waiver will not relieve the Government of answering according to the judgment obtained for damages established. The same assumption will apply in the event that a medical officer is proven negligent. This should not be a startling or disconcerting realization for the reason that negligence thus established would depend upon the testimony of persons who qualify as specialists in the field. Such testimony would be anticipated to establish any rules or reason applicable to use of radioisotopes in diagnosis and treatment. In the second sense the execution of a statement similar to Enclosure (2) constitutes evidence, if properly completed, that the patient was aware of and accepted any possible risks involved whether because of the modernity of the treatment or because of other circumstances such as the patients own condition (provided the patient knows the facts).

6. In view of the foregoing, there is no legal objection to the use of the proposed forms. Any instructions to medical activities in the field should state as briefly as possible the reasons for having such statements executed. At the same time medical officers should be reminded that liability depends upon negligence in the performance of duty and that appropriate care in the use of any remedies whatever should be required. What constitutes appropriate care will again be a question which may be answered only by specialists in the field. It is not necessarily incumbent upon the Bureau to attempt to obtain a specified definition of appropriate care under the circumstances. There will be, however, some indications from experience of procedures which should not be used and knowledge of these procedures as acquired should be promulgated to the activities concerned with related types of diagnoses and treatment.

7. Enclosures (1) and (2) are returned herewith. There is also returned Commanding Officer, U. S. Naval Hospital, San Diego letter of [illegible] Sep 1951 to the Bureau.

LOREN B. POUSH

2

[redacted] Code [redacted]

SUBJECT: Proposed Means of Proper Authorization and Safegu ard in Use of Radio-Isotopes.

Encl: (1) Copy of PERMISSION TO USE RADIO-ISOTOPES
(2) Copy of AUTHORIZATION BY THE ISOTOPE COMMITTEE" FOR THE USE OF A RADIO-ISOTOPE

1. Enclosures (1) and (2) forwarded for comments as to legal value.

D.E.DEMENT

7212 — X 63656 Plant
Referred to Radio Section X 63020 AE Tipton File A16-3/NN
Bring 7 Basement if Below 3 = 03

COPIED: 7/6/94
RECORD GROUP: #52
ENTRY: #15C
FILE: A16-3/DD
1951

ISOTOPE

Date:

1. It is the request of this patient _____ that (he-she) be given a (tracer-therapeutic) dose of _____ by the staff of the Radioisotope Laboratory. This laboratory is supervised by the Hospital Board for the Control of Radioisotopes in Human Patients.

2. The patient understands that all redioisotopes used in this hospital are obtained from the Atomic Energy Commission for research projects.

3. The method of administration and general plan of study have been approved by the Medical Committee of the Atomic Energy Commission and the local Committee for the Use of Radioisotopes in Human Patients.

4. It is to be understood that the U. S. Navy, the Naval Hospital at Bethesda, Maryland, its agents and its personnel assume no responsibility for the results or effects of this study nor of its interpretation.

(Signed) _____

(Signed) _____

(Witness) _____

(Witness) _____

1. This study determines the ability of the thyroid to concentrate iodine. The amount and distribution of the radioiodine is measured by means of Geiger-Muller counters on the skin over the thyroid gland. The amount of radioiodine excreted in the urine is measured in specimens saved over a period of 48 hours.

2. The referring doctor should discuss with the Radioisotope Laboratory recent use of the following:
(a) Thyroxine, propylthiouracil, or any type of hormone therapy
(b) Iodine containing preparations:
(1) Lugol's solution or syrup of Hydriotic acid.
(2) Diodrast (I.V. and retrograde pyelograms, arteriograms, injection of sinus tracts).
(3) Lipiodol (Bronchograms, injection of sinus tracts).
(4) Cholografin (Myelograms).
(5) Priodox (Gall Bladder series)
(6) KI (Expectorant cough medicines, e.g. Brown's Mixture).
(7) Argyrol (Bladder and urethral infections)
(8) Thiocyanates (Hypertension therapy)
(9) Thimerosin (Mercurial Diuretic)
(10) Diodoquin and Chiniofon (Antidiarrheals).
(11) Diiodofluorescein (Renal tumor studies).
(12) Vioform (Skin ointment)
(13) Tincture of Iodine (Skin antiseptic)

3. Restrict the following foods as much as possible from 24 hours before and 48 hours following the study: Iodized salt, fish, shellfish, liver, nuts (e.g. nuts and walnuts), turnips, bananas, spinach, peaches and pears.

4. Avoid all enemas and use of laxatives on this patient for 24 hours preceding and the first 24 hours of the study. Please report if patient has loose or frequent stools, as it requires us to make tests of the stools for possible radioiodine elimination by this route.

5. Urine Collections:
Save all urine from the time of the dose on for 48 hours in containers as listed below. Save in accordance with the labels on the containers furnished. Use only the containers furnished by this laboratory.
Collection schedule will be:
12 hour specimen
24 hour specimen
48 hour specimen.

6. If there are any questions, call the Radioisotope Laboratory [illegible].

7. Time of dose _____

No food or drink after _____ hour _____ day _____ month [illegible]
Please insert this page as part of the Patient's chart.

_____
Head, Radioisotope Laboratory

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ENTRY: #15C
FILE: A16-3/PD
1951

Name: _____ Hospital Admission No. _____

Autopsy No. _____

Isotope Administration:

Isotope	Treatment or Tracer	Dose	Date Administered

Results of Radiac Survey:

Highest measurement external skin surface _____

Highest measurement inside body cavity;

With viscera intact _____

With viscera removed _____

Highest measurement external skin surface after viscera removed _____

Remarks: _____

_____

This certifies that the remains of _____ have been examined by Radiac Survey and is below the accepted tolerance dose-rate of 6 mr/hour. There will be no health hazard involved by the mortician performing the embalming provided he wears rubber gloves.

_____

Radiac Survey Officer

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RECORD GROUP: #52
ENTRY: #15C
FILE: A16-3/PP
1951

[redacted] TRACER CASE #_____

RADIOISOTOPE LABORATORY REPORT

_____TRACER STUDY #_____

Patient's Name_____ ____ ____ ____
Last First Initial Age Weight Height

_____ _____ _____
Date of Request Rank or Rate Ward or Out-Patient

_____
Provisional Diagnosis

Reason for Tracer Study:

_____
Doctor Requesting

_____
Head, Radioisotope Laboratory

_____
Chief of Radiology

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RECORD GROUP: #52
ENTRY: #15C
FILE: A16-3/PD
1951

[redacted], MARYLAND THERAPY CASE #_____

RADIOISOTOPE LABORATORY REPORT

_____THERAPY #_____

Patient's Name_____ ___ ___ ___
Last First Initial Age Weight Height

_____ _____ _____
Date of Request Rank or Rate Ward or Out-Patient

_____
Provisional Diagnosis

Rationale for Radioisotope Therapy:

_____
Doctor Requesting

Radiation Tissue Dose

Estimated Tumor Dose:
Estimated Skeletal Dose:
Estimated Total Body Dose:

_____
Head, Radioisotope Laboratory

_____
Chief of Radiology

COPIED: 7/6/94
RECORD GROUP: #52
ENTRY: #15C
FILE: A16-3/PD
1951

DISPOSITION FORM

FILE NO.	SUBJECT
MEDDH	Draft of "Agreement with Volunteer"

TO Chief, Legal Office, SGO FROM Med Res & Dev Bd, SGO DATE 5 Jan 52 COMMENT NO. 1
Col Rapalski/65997

1. The attached is a copy of an agreement to be used by Dr. George S. Hirick in his use of human volunteers from the inmate population of the Maryland Penitentiary, Maryland House of Correction, and Maryland State Reformatory for Males.

2. Request clearance for approval of this agreement by the Armed Forces Epidemiological Board.

ADAM J. RAPALSKI
Colonel, M. C.
Administrator,
Armed Forces Epidemiological Board

Incl.
Cpy, draft

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TO	FROM	DATE	COMMENT NO. 2
The Judge Advocate General Department of the Army	Legal Office Surgeon General's Office Department of the Army	21 Jan 1952	Lt Col Sheehan 62501

Your comments are requested on the attached draft of "Agreement with Volunteer" which is to be used with a medical research contract with The Johns Hopkins University, Baltimore, Maryland.

FOR THE SURGEON GENERAL:

GERARD J. SHEEHAN
Lt Col MSC
Chief, Legal Office

Incl
N/c

DD FORM 1 FEB 50 96 REPLACES NME FORM 96, 1 OCT 48, WHICH MAY BE USED.

COPIED: 12/2/94.
RECORD GROUP: #334
ENTRY: #14
FILE: Commission on Liver Diseases — Human Volunteers for Hepatitis Studies — Feb 1948 on

THE JOHNS HOPKINS UNIVERSITY
SCHOOL OF MEDICINE

AGREEMENT WITH VOLUNTEER
WHICH ALL MUST BE SIGNED BY THEMSELVES:

THAT, I _____ being of

_____ years of age do hereby voluntarily apply for permission to participate in a study of what is generally known as the virulency of hepatitis. This study, as it has been explained to me, is to determine the effects of various viruses on the human liver. This study is being made under a contract between the Commission on Liver Diseases of the Armed Forces Epidemiological Board and the Johns Hopkins University in Cooperation with the Maryland Board of Correction.

I understand that I will be required to undergo a physical examination and certain tests of my liver's function in order to ascertain if I am a suitable candidate. Upon acceptance as such volunteer to submit to inoculations and such other procedures as may be necessary to carry out the study, to repeat a physical examination and liver function studies as often as deemed necessary by the physicians in charge, and, if infection occurs, to such treatment as is provided. I agree that the physician-in-charge shall be the sole judge of the duration of the period of isolation and hospitalization necessary. It is further understood that the Commission on Liver Diseases shall be the sole judge as to whether any illness occurring subsequent to the termination of this experiment is or is not the result of the aforesaid experiment and is or is not sufficiently severe to require further medical care and the necessary duration thereof.

The procedure, potential benefits to science and risks of participation in the study have been explained to me by the physician-in-charge, Dr. George C. Kimick, and are understood by me, and I hereby assume all risks of such participation. I agree to cooperate to the fullest extent with the physicians conducting the study.

I understand that at the conclusion of my satisfactory participation in the study, I am to be furnished an appropriate Certificate of Merit and a statement of my voluntary cooperation in the study. The fact that I have thus rendered voluntary service to humanity will be placed in my official record. I understand that the sum of $0.50 per day while I am a part of this study will be deposited to my account at the Maryland State Reformatory, for value.

In consideration of being allowed to be part of such a study, I, acting for myself, and for and in behalf of my heirs, personal representatives and assigns, do hereby release the Johns Hopkins University, the

Maryland Board of Corrections and the Armed Forces Epidemiological Board and their personnel from all liability, including; claims and suits at law or in equity, for any injury fatal or otherwise, which may result from my participation in this study.

IN WITNESS THEREOF, I have hereunto set my hand this

_____ day of _____, 1952.

_____ Witness

_____ Name of Volunteer

_____ Witness

Accepted: _____ Physician-in-charge

Approved: _____ Warden

COPIED: 12/2/94
RECORD GROUP: #334
ENTRY: #14
FILE: Commission on Liver Diseases - Human Volunteers for Hepatitis Studies - Feb 1948 on

FINCA 019 25 April 1952

MEMORANDUM FOR FILE:
SUBJECT: Research and Development Contracts - Medical Investigations.

1. Upon receipt of the inquiry from the Chemical Corps this office contacted the Surgeon General, Lt. Col. Sheean, Legal Section, Ext. 6251, Room 1060A of Main Navy and he advised that they take a form of release from such volunteers before they are used as human "guinea pigs" by the contractors with the United States. Seemingly all the contracts are executed with hospitals or universities and are generally on a cost basis; on occasion there is a cost-plus-a-fixed-fee contract with a commercial organization. Copy of the release was forwarded to this office.

2. I talked to a Mrs. Johnston, Surgeon General, Ext. 65111 and she advised that she would send to me specimen contract forms. From her I understood that they were having considerable difficulty in connection with possible losses of this kind and that in general they are not too convienced that their contract is a good one.

3. Then talked to Col. John R. Wood, Ext. 65976, Chairman of the Research and Development Board of the Surgeon Generals office. Col. Wood advised that they just had a situation in which the contractor, the Massachusetts General Hospital, inquired as to whether or not the Government would reimburse as a cost under the contract expenditures they must make to said volunteers because something may go wrong during the investigation. This matter is still pending and has not been resolved. There is no special clause in the contract on this subject and it is just subject to the general rules of ASPR 15, Contract Cost Principle. From Col. Wood I learned that generally the contractors do compensate their volunteers; students and prisoners are compensated to a degree and as a general proposition all persons who submit themselves to these tests are compensated in varying amounts, depending upon the nature of the tests being run, sums involved running from $25 to $250. The only exception is that they do not pay military personnel, and in that instance grant additional leave etc. Generally speaking these hazards are not severe. Up to this time they have had no unfortunate occurrence that they know of. The tests are largely quantitative rather than qualitative; by that is meant that they use human subjects to find out what percentage of them will have a favorable as against an unfavorable reaction; on occasion however there is some disease that cannot be tested by animals but they must use a human subject for purposes of determining effect in the first instance. Col. Wood advised me that they knew of only a couple of instances in which there has been a claim on behalf of anyone after signature of the so-called releases. One was a prisoner at Illinois but that situation resolved itself because it was shown that the prisoner destroyed the releases and then denied that he had signed them; also the claim was made by the prisoner against the doctor who actually administered it and not the contractor. As far as the Colonel knows nothing came of it and it was disposed of although he did not know what court action took place.

Seemingly also there was one instance that occurred at Massachusetts General Hospital in which they were experimenting for shock treatment. However, that seemed to have worked out satisfactorily also.

4. I talked to Mr. Shetley of the Navy insurance section and he was going to investigate as to what the Navy did in comparable circumstances. He believed that they also took those so-called releases.

5. I then talked to Mr. Fredricks by the wire. I advised him that generally we could not provide any workmen's compensation form of policy to cover risks of this kind. If the subject were an employee of the contractor, then he is already covered under the workmen's compensation policy of the contractor. If the subject were not an employee, then of course it would be impossible to work up such a system as he has in mind; he advised that the contractors do not want to consider these people as employees which is understandable. In connection with use of FD-502, I told him that it could be possible that this form could be used but only by employees of contractors with the United States. I sent to him a group of the application forms and also told him that this was to be used only when the Government of the United States reimburses the cost thereof and that we do not intend that it should be encouraged because each time the policy is issued the Government pays the cost of it. Mr. Fredericks advised that they have had no difficulty in recruiting people up to this time. He is not sure whether or not it is necessary to voluntarily extend benefits beyond compensation paid to the volunteer. He advised that this matter has been current for a considerable length of time and they are merely giving it consideration again. He states that they do have a little case now in which a contractor with the Chemical Corps wants to reimburse one of the subjects for some additional time he lost because he was sick for a longer period of time than anticipated; as a consequence the contractor wants the Army Chemical Corps to reimburse him such expenditure if he makes it. That matter has not been resolved as yet. I also advised him as to whether or not the Department of the Army wants to go beyond legal liability in furnishing benefits to these people if something should take place is a matter for policy determination by the Chief of the Chemical Corps and perhaps the Army Chief of Staff. With that he concurred. Mr. Fredericks is going to send us a copy of his specimen contract and I advised him that I would inform him of any developments unearthed in our investigation as to how this matter can best be handled.

L. M. [illegible], Chief
Contract Insurance Branch

FEDERAL SECURITY AGENCY • Public Health Service
NATIONAL INSTITUTES OF HEALTH • Bethesda 14, Md.

NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES
NATIONAL CANCER INSTITUTE
NATIONAL INSTITUTE OF DENTAL RESEARCH
NATIONAL HEART INSTITUTE
NATIONAL INSTITUTE OF MENTAL HEALTH
NATIONAL MICROBIOLOGICAL INSTITUTE
NATIONAL INSTITUTE OF NEUROLOGICAL DISEASES AND BLINDNESS
THE CLINICAL CENTER
DIVISION OF RESEARCH GRANTS

April 30, 1952

Rear Admiral Winfred Dana
Medical Corps, U.S.N.
The Pentagon
Washington 25, D. C.

Dear Doctor Dana:

In accordance with our telephone conversation of this afternoon I am enclosing a copy of the draft statement which we have developed. As I mentioned to you, this is still in draft stage and we would appreciate any ideas that you may have after looking it over.

At our latest meeting we decided to delete a clause under point No. 6 reading "and after participating investigators have also agreed to serve as subjects." Despite the possible moral and ethical justification for such a clause, we felt that it was unrealistic to make such a flat requirement. We are now thinking of substituting for that deleted clause something of this sort: "When the investigator cannot in good conscience ask others to undergo a risk that he himself would not be willing to accept, and when his participation will contribute to the scientific value of the investigation, he should agree to serve as a subject." I cannot say what our final decision will be on this question, and your advice will be most helpful.

I hope that you find this draft an aid in your thinking on this difficult matter.

Sincerely yours,

Charles V. Kidd

Charles V. Kidd
Director
Research Planning Branch

Enclosure

WNRC: 17-28 October 1994
ACCESSION: 68A-6375
RG #330
File Name: Volunteers For Experimental Research (52-53)
Box # 1

REVISED DRAFT
4/28/52

ETHICAL PRINCIPLES UNDERLYING INVESTIGATIONS INVOLVING HUMAN BEINGS

Investigations involving human beings — often entailing medical procedures or therapy that are substantially different from accepted general medical practices — are an essential component of medical research. This offers the only means of acquiring the new information necessary to solve the problems of the diseases and disorders that afflict man. Ethical and scientific considerations dictate, however, that these investigations must be undertaken only after mature thought, under rigorously defined and controlled conditions, and under circumstances which will minimize the dangers of predictable or unpredictable hazards. The basic principle upon which all such investigations rest is that human beings have inalienable rights that supersede all other considerations that may be raised in the name either of science or of the general public welfare. Therefore, the responsibility of the physician for the physical and mental well being of persons in his care and for observance of the ethics of his profession cannot be overridden by any element of study or research which is interjected into the relationship between the physician and persons in his care.

Within these general principles, the following guide lines, which should be considered as a group, must be observed:

1. The person who is competent to give consent to an investigative procedure must do so. He must have legal capacity to give consent and be able to exercise free choice, without the intervention of any element of force, fraud, deceit, duress, constraint or coercion. He must have sufficient knowledge and comprehension of the nature of the investigation to enable him to make an

derstanding and enlightened decision. He must therefore be told the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; the inconveniences and hazards reasonably to be expected; and the effects upon his health or person which can reasonably be expected to come from his participation in the investigation. He should understand, furthermore, that by his participation he becomes a co-investigator with the physician.

In the case of a person who is not competent to give consent, the consent of his legal guardian must be secured after the guardian has been given the information outlined above. The over-all conditions surrounding investigations involving persons who are not competent to give consent must be such that benefit may be expected to accrue to him.

The responsibility for ascertaining the quality and acceptability of the judgment made by one who consents to participate in a contemplated investigation, and for accepting or rejecting such a consent, rests immediately upon the physician responsible for the medical care of the person involved and ultimately upon those to whom the physician is administratively responsible.

2. The patient (or, in the case of a person not competent to choose, his legal guardian) should be at liberty to withdraw his consent and to cease participation in the study at any time and for any reason, except when abrupt discontinuance would clearly endanger his health or life.

3. When studies involve human beings, the physician is obliged to seek, and the institution with which he is affiliated is obliged to provide, competent advice as to the acceptability of all elements of every proposed investigation, both as originally planned and as they evolve, in relation to the welfare of the patient or subject.

4. Investigations involving human beings should be undertaken only after earlier study of animals, or the clear irrelevance of animal studies to humans, preclude the probability that a definitive answer can be obtained by work limited to animals. Moreover, an investigation should not be undertaken until the hazard to the human participant has been determined as well as is reasonably possible by earlier study with animals or from clinical experience.

5. The investigation should be so planned and conducted as to avoid all physical and mental suffering and injury except that which is indispensable to the investigation.

6. The physician responsible for the care of the patient must terminate the investigation if he has cause to believe that continuation may result in an irreversible change, disabling injury or a fatal outcome. However, in those rare circumstances under which an investigation involving more than a negligible probability of irreversible change, disabling injury or a fatal outcome is considered, the investigation may be undertaken if it appears to be the only way to achieve a major medical advance, but then only after all alternatives have been fully exhausted, and after participating investigators have also agreed to serve as subjects.

7. The investigation should be conducted only when physical facilities to protect the patient are adequate, and only by scientifically and medically qualified persons. The highest degree of good faith, judgment, skill and care should be required of those who conduct or engage in the investigation.

JVK:ab

AFR 80-22
1-3

AIR FORCE REGULATION
NO. 80-22

DEPARTMENT OF THE AIR FORCE
WASHINGTON, 1 JULY 1952

RESEARCH AND DEVELOPMENT

Clinical Research

Sup. to AFR 80-22, 1 Oct. 1952

1. Purpose and Scope. This Regulation establishes a program and prescribes the policies, procedures, and responsibilities for sponsoring and supporting clinical research at Air Force hospitals, dispensaries, and other clinical medical facilities. It is applicable to all Air Force medical activities and facilities.

2. Policy. The Air Force policy is to encourage and support clinical research by officers of the Medical Service, USAF, at any Air Force medical facility for the purposes of improving patient care; improving clinical techniques; and increasing the efficiency of the Medical Service, USAF. To this end, services of consultants, publication services, funds, or special items of equipment will be made available through the USAF School of Aviation Medicine to support approved research.

3. Definition. Any research proposal is eligible for support which promises to improve Air Force medical care, including examination, diagnosis, treatment, and care, establishment of new procedures or development of new equipment, modification of existing methods, and hospital or field testing of methods or equipment. Such research must be performed by or in association with medical, dental, nurse, veterinary, or medical service officers as a byproduct of their regular duties. No additional personnel will be authorized the initiating activities to support such research.

4. Responsibility:

a. The "initiating officer," who is authorized to communicate direct with the Commandant, USAF School of Aviation Medicine, will describe the need for the proposed investigation, search the scientific literature for related studies, and prepare a proposed research design and project proposal.

b. The base surgeon or officer in charge of the facility will be the "responsible officer." He will make every effort to maintain progress of approved investigations; he will insure that regular activities of his facility are not impaired; and he will be responsible for utilizing equipment and expending funds allotted for the investigation. If the initiating officer is transferred the responsible officer will designate a new "principal investigator" to carry on the investigation.

c. The USAF School of Aviation Medicine will provide funding and monitorship over the program and each investigation.

5. Procedure:

a. The responsible officer will communicate direct with the Commandant, USAF School of Aviation Medicine, Randolph Air Force Base Randolph Field, Texas, using the subject title "Proposal for Clinical Research, AFR 80-22." The proposal, in original and five copies, will contain the following information:

(1) Statement of the problem.

(2) Requirement, in terms of Air Force needs, which justifies the investigation.

(3) Brief summary of the background of the investigation including major references to related research and a statement of the expected improvement in the Medical Service, USAF.

(4) Research design, which should be as detailed as possible, with description of methods to be used, controls, size of sample, and other information needed for adequate evaluation by experienced scientists.

(5) Name, grade, and title of responsible officer, principal investigator, and other investigators, as well as information regarding advanced training, publications, and so on.

(6) Facilities, both required and available, for the proposed research, to include experimental subjects.

(7) Items of nonstandard equipment to be provided by the USAF School of Aviation Medicine, with approximate cost and suggested source.
(8) Total estimated cost.
(9) Duration and time phasing of proposed investigations. Investigators will be encouraged to design research projects that can be completed in less than one year.

b. The research proposal will be evaluated by the Research Council of the USAF School of Aviation Medicine which will notify the responsible officer of approval or disapproval of the investigation or will suggest modification and resubmission of the proposal.

c. Research proposals, when approved by the Research Council of the USAF School of Aviation Medicine, will be classified as *projects* or *tasks* as defined in AFR 80–13. Projects will be approved by higher headquarters in accordance with AFR 80–20. When classified as a task of a previously approved project, the action of the Research Council will be considered final.

d. Those investigations approved may be aided with funds to the extent available and/or with special items of equipment. Such funds and items of equipment will be utilized solely to carry out the approved research.

e. The USAF School of Aviation Medicine will provide all necessary research and development project data to the Commanding General, Air Research and Development Command, in accordance with AFR 80–7.

6. **Funds.** Funds may be made available to the medical officer in charge of the facility where the research is to be accomplished by AF Form No. 405, "Obligation Authority," citing the fund account to be obligated and stipulating the purpose of expenditures, amounts, and time limits. No funds will be made available for hiring additional personnel or for travel nor will there be any prorating of personnel costs between two or more fund areas. Responsible officers or investigators will not enter into contractual agreements with outside agencies for purposes of performing portions of the investigation under the provisions of this Regulation. Contracts may be let only with the approval of the USAF Scho of Aviation Medicine.

7. **Equipment.** Nonstandard and special items of equipment may be purchased by the USAF School of Aviation Medicine and shipped to the using activity. All items of equipment procured under the provisions of this Regulation will be transferred to the USAF School of Aviation Medicine, at its direction, upon completion or termination of the research.

8. **Scientific Reports.** Research accomplished will be included in the technical reports of the USAF School of Aviation Medicine and recognition will be accorded both author and organization where the research was accomplished. Subsequent publication in military or civilian professional journals will be encouraged. Progress reports will be submitted as required by the USAF School of Aviation Medicine.

BY ORDER OF THE SECRETARY OF THE AIR FORCE:

N. F. TWINING
Acting Chief of Staff
United States Air Force

OFFICIAL:

K. E. THIEBAUD
Colonel, USAF
Air Adjutant General

DISTRIBUTION:
D

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THE JOINT CHIEFS OF STAFF
WASHINGTON 25, D.C.

SECRET

SM-2077-52
3 September 1952

MEMORANDUM FOR: Chief of Staff, U.S. Army
Chief of Naval Operations
Chief of Staff, U.S. Air Force

Subject: Security Measures on Chemical Warfare and Biological Warfare

1. The Joint Chiefs of Staff have considered the recommendation by the Secretary of the Air Force that action be taken to "tighten security measures on Chemical Warfare (CW) and Biological Warfare (BW) but not to extent of over-classification with the resultant damage to our accelerated program". In connection with CW, the Joint Chiefs of Staff note that only part of the field of CW pertaining to nerve gases is of such sensitivity as to require a special guide for its security classification and therefore the term CW as used herein applies only to the nerve gases. The Joint Chiefs of Staff note that information concerning BW and CW is being more widely disseminated than is necessary or is desirable from a security point of view. The Joint Chiefs of Staff, after examining the current over-all policy on security classification of military information and the security classification policies concerning BW and CW, agree that the policies furnish adequate guidance for safeguarding these areas of information and consider that within the framework of the existing policies action can be taken to curtail unnecessary dissemination of BW and CW information. Accordingly, the Joint Chiefs of Staff are of the opinion that, in the interest of increased security, responsible agencies should re-examine their procedures for implementing the current policies and keep under continuing review the following:

a. Measures to insure adequate classification under the presently effective over-all security classification policy and the specific security policies governing classification of matter concerning BW and CW.

b. Measures to insure that classified BW and CW documents and information are made available to authorized

personnel only on a "need-to-know" basis with determination in each case reserved to the highest practicable level of command in each Service concerned.

2. The Joint Chiefs of Staff further consider that responsible agencies should:

a. Impose stringent controls over visitors to activities involved in the BW and CW programs. Visits by individuals or groups for indoctrination purposes should not normally be authorized. Rather, consideration should be given to devising a means to conduct essential indoctrination programs at places other than where BW or CW research and development work is being performed and possibly by personnel not directly concerned in this work. Conversely, this should not be construed to exclude personnel who are actually engaged in the furtherance of the BW and CW programs.

b. Maintain under continual surveillance positive measures to insure thorough security indoctrination of all personnel, and in particular, civilian scientists assigned to the BW or CW programs. And further insure that all such personnel are debriefed prior to assignment to other duties outside these fields or upon termination of employment in connection therewith.

c. Impose a time-lag on publication, sufficient to provide security for current research, when reviewing BW and CW material prepared for unclassified publication by personnel connected with the BW or CW programs.

d. Insure, insofar as practicable, that all published articles stemming from the BW or CW research and development programs are disassociated from anything which might connect them with U.S. military endeavor.

For the Joint Chiefs of Staff:

SIGNED

W. G. LALOR,
Rear Admiral, U.S. Navy (Ret.),
Secretary.

Copies to: Asst C/S, G-3
Secy to CNO (JCS)
Director/Plans, AF
Commandant Marine Corps
Director, J/S

(Further implemenation JCS 893/18)

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CORRECTED: 11/29/94.
RECORD GROUP: #319
ENTRY: G-3/DCSOPS
FILE:

MEDDH	Applicability of Section 5, Public Law 557 - 82nd Congress	
Chief, Legal Office SGO	Armed Forces Epidemiological Board	14 Oct 52 Col Rapalski/65997

1. The Armed Forces Epidemiological Board has raised the question as to a practical problem in conjunction with Public Law 557 - 82nd Congress. Under its sponsorship, the Armed Services are supporting crucial medical research in which human volunteers in Federal and State prisons are involved.

2. The particular question that has been raised is whether Section 5 of the above cited Law is applicable to afford relief to the immediate dependents of such prisoner volunteers when as a result of these experiment they should die.

3. It is requested that information be furnished upon which to base a reply to the questions asked by the Board, and information as to how, if it is applicable, such provisions can be made in the contracts.

FOR THE ARMED FORCES EPIDEMIOLOGICAL BOARD:

Incl.
Cpy P.L. 557

ADAM J. RAPALSKI
Colonel, M. C.
Administrator,
Armed Forces Epidemiological Board

ARMED FORCES EPIDEMIOLOGICAL BOARD

MEDDH

MEMORANDUM FOR: MEMBERS OF THE ARMED FORCES EPIDEMIOLOGICAL BOARD
DIRECTORS OF ALL COMMISSIONS

SUBJECT: Applicability of Section 5, Public Law 557 - 82nd Congress

1. As instructed by the Board at its Fall Meeting an inquiry was directed to the Chief of the Legal Office as to the applicability of Section 5, Public Law 557 - 82nd Congress in affording relief to the immediate dependents of prison volunteers.

2. The following reply has been received:

"This law does not directly affect the prisoner or next-of-kin. This law is designed to indemnify contractors against any liability resulting from injury to persons or damage to property arising out of the direct performance of a research and development contract. The sense of Congress, as taken from the legislative history of this act, is as follows:

'Section 5 provides authority for the military departments to agree to indemnify contractors against liability and loss resulting from injury to persons or damage to property arising out of the direct performance of a research and development contract, to the extent that such losses are not compensated by Insurance or otherwise. In many cases, contractors are reluctant to undertake a research or development contract involving extremely hazardous new developments without securing adequate protection in the event of liability resulting from claims made as a result of damage from those experiments. No provision can be made for such protection by including a reserve in the contract price, and the cost of insurance, if at all obtainable, would be prohibitive. The solution is for the Government to agree to indemnify such a contractor, subject to the safeguards provided in this section.'

From the wording of the law, and from the above quoted legislative history, it can be determined that this provision was aimed at private contractors as distinguished from Governmental agencies. It is aimed at those functions or experiments which are unusually hazardous for which the contractor cannot obtain liability insurance, and it is a direct indemnification to the contractor and not to the individual human guinea pig. The charge of claims, therefore, would be for the next-of-kin of the deceased person to make a claim against the contractor. In such an instance, the contractor is liable and, should he be forced by decision of court to pay on a judgment rendered in behalf of the next-of-kin, then, under the law the Government would reimburse the contractor for the amount of the judgment."

R

COPIED: 11/30/94
RECORD GROUP: #334
ENTRY: #13
FILE:

"The wording of the law indicates that the provisions of Section 5 would extend to prisoners and their next-of-kin. This can be deduced from the quoted part of the law as follows:

'With the approval of the Secretary concerned, any contract of the military departments for research and development * * * (1) Liability on account of claims * * * by third persons, including employees of the contractor, for death, * * *.' "

"If a contract for such research were entered into by the Armed Forces with another Governmental agency, it would seem that there would be no need for a clause in the contract to indemnify the contractor. In this case, the contractor being another Governmental agency, the Government only would be liable. If such a contract were let to a private concern or establishment, then such a clause of indemnification would be entirely proper. In such an instance, a clause modeled in substance as follows, would be appropriate:

'It is hereby agreed that the Government will indemnify the said contractor against either or both of the following, to the extent that they arise out of the direct performance of said contract and are not compensated by insurance or otherwise: (1) Liability on account of claims (including reasonable expenses of litigation or settlement of such claims) by third persons, including employees of the said contractor, for death, bodily injury, or loss of or damage to property, arising as a result of a risk defined in the contract to be unusually hazardous: Provided, that the contractor shall immediately give notice to the Government of any suit or action filed or any claim made against the said contractor, with respect to any alleged liability for such death, bodily injury, or loss of or damage to property, and for control of or assistance in the defense of any such suit, action, or claim, by the Government, at its election; and (2) loss of or damage to property of the said contractor arising as a result of any risk defined in this contract to be unusually hazardous: And provided further, that no payment shall be made by the Government under the authority of Section 5, Public Law 557 - 82nd Congress, unless the amount thereof shall first have been certified to be just and reasonable by the Secretary concerned or by an official of the department designated for such purpose by the Secretary.' "

3. The Medical Research and Development Board, Office of the Surgeon General, Department of the Army, proposes to use the above clause, or one very similar to it, as soon as it is approved by The Judge Advocate General, in drawing up future contracts, and in modifying old contracts as they are renewed to include this added clause.

FOR THE ARMED FORCES EPIDEMIOLOGICAL BOARD

ADAM J. RAPALSKI
Colonel, M. C.
Administrator,
Armed Forces Epidemiological Board

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DEPARTMENT OF DEFENSE

SECURITY INFORMATION

SECRET

Research and Development Board

Washington, D.C.

COMMITTEE ON CHEMICAL WARFARE

Transcript of the Fourteenth Meeting
Held 10 November 1952, in Room 3E-1060
The Pentagon

* * * * *

Conference Reporting Section
Reported By: Gasdor, Martin & Self
Extension 73252 Room 3C-116

SECURITY INFORMATION

can we come to them, but I'd be glad to have your comments on any one of them.

COLONEL BAYLISS: We have no disagreement, I don't believe, with any of these. I think there is a little inconsistency in Paragraph 33, though, when we come to that.

THE CHAIRMAN: If there is nothing on 31 or 32 --

DR. WORTHLEY: Mr. Chairman, Paragraph 31 makes reference to proposals under consideration by the Armed Forces Medical Policy Council .

Since this was written -- in fact just the other day -- we received from the Medical Armed Forces Medical Policy Council, a statement of their recommendations to the Secretary on this matter, and these are being circulated to the RDB committees concerned for consideration and comments. It just happens that they strike us, you might say, at the psychological moment, and I wonder, in consideration of this question, which is a rather important one, in the program, if you'd care to have this document of the Armed Forces Medical Policy Council read?

THE CHAIRMAN: Is it long? [Laughter]

DR. WORTHLEY: About a page and a half.

THE CHAIRMAN: Are you agreeable, gentlemen? The answer is yet. All right.

DR. WORTHLEY: This is on the subject of the use of

human volunteers in experimental research. Dr. Casberg advises Mr. Whitman this way: "The attached recommendations and supporting conditions pertaining thereto are forwarded for your information and comment. The Medical Policy Council approved the adoption of the recommendations at the 13 October 1952 meeting. These are the recommendations: In view of previous recommendations of the Medical Policy Council that human subject be employed as the only feasible means for realistic evaluation and/or development of effective preventive measures of defense against atomic and biological or chemical agents. The Council further recommends that the following policy be affirmed with respect to the participation of personnel of the Armed Services in the atomic, biological and chemical warfare research programs: (1) By reason of the basic medical responsibility in connection with the development of defenses of all types against atomic, biological and/or chemical warfare agents, Armed Services personnel and all civilians on duty at installations engaged in such research shall be permitted to actively participate in all phases of the program. Such participation shall be subject to the following conditions: (1) Voluntary consent of the human subject is absolutely essential. This means that the person involved should have legal capacity to give consent and should

be sosituated as to be able to exercise free power of choice without the intervention of any element of force, fraud, deceit, duress overreaching, or other ulterior of constraint or coercion. He should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding decision. This latter element requires that before the acceptance of an affirmative decision by the experimental subject, there should be made known to him, the nature, duration and purpose of the experiment, the method and means by which it is to be conducted, all inconveniences and hazards reasonably to be expected, and the effects on his health or person which may possibly come from his participation in the experiment. The consent of the human subject shall be in writing. His signature shall be affixed to a written instrument setting forth substantially the aforementioned requirementand shall be signed in the presence of at least one witness and shall attest to such signature in writing. The duty and responsibility for ascertaining the quality of the consent rests upon each individual who initiates, directs or engages in the experiment. It is a personal duty and responsibility which may not be dlegated to another.

(2) The experiment should be such as to yield fruitful

results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature.

(3) The experiment should be so designed and based on the results of animal experiments and a knowledge of the natural history of the disease or other problems under study, that the anticipated results will justify the performance of the experiment.

(4) The experiment should be so conducted as to avoid all unnecessary physical and mental suffering.

(5) No experiment should be conducted where there is a priori reason to believe that death or disabling injury will occur; except, perhaps, in those experiments where the experimental physicians also serve as subjects.

(6) The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.

(7) Proper preparation should be made and adequate facilities provided to protect the experimental subject against even the remote possibility of injury, disability or death.

(8) The experiments should be conducted only by scientifically qualified persons. The highest degree of skill and care should be required through all stages of the experiment of those conducting or engaging in the experi-

(9) During the course of the experiment, the human subject shall be at liberty to bring the experiment to an end if he has reached the physical or mental stage where the continuation of the experiment seems to him to be impossible.

(10) During the course of the experiment, scientists in charge must be prepared to terminate the experiment at any stage if he has probable cause to believe that the exercise of good faith, superior skill and careful judgment required of him, that a continuation of the experiment is likely to result in injury, disability or death to the experimental subject.

(11) Whereas, prisoners incarcerated in field institutions, may and have been used if the required conditions are met, prisoners of war will not be used in human experimentation."

DR. JOHNSTONE: If they can get any volunteers after that I'm all in favor of it.

[Laughter]

THE CHAIRMAN: Yes, Colonel Bayliss.

COLONEL BAYLISS: I might point out that we have been running voluntary experiments for a long period of time. We do have difficulty in getting volunteers. Most of the volunteers are from our own medical laboratories, and

When we try to go outside of medical laboratories, we have great difficulty, but we gotten volunteers for a limited number of experiments that we have conducted, mostly from our own group. The moment we try to go out of our own place, even for an experiment that there is no danger at all, go to something like the Training Command, we are immediately turned down. It takes too much time and they can't be bothered with it. That always happens, and it doesn't really give us any means of obtaining volunteers, other than medical laboratories, but it might be difficult to say that there was no coercion used. They worked there. Their salary depends upon it.

If we go over to Chemical and Radiological Laboratories we getno volunteers. If we go to Research and Engineering Command, we get no volunteers. Within our own place, though, we do get some. [Laughter].

Now there is no reward for volunteering; that's the whole thing. The man who is an office man, he doesn/t get a day off. There is no mechanism whereby we can get them. We can't get any extra pay for them. If they should, for some reason, die during these experiments, the people, I might point out, have died from such things as injecting minute amount of novocain. Small amounts of ether will kill an individual who is sensitive to it. You never know

when you are going to run into somebody who is sensitive. Is there any protection for the man who dies during such an experiment, even though there is relatively little danger, or is there any protection for the experimenter in the legal courts? That is the whole thing that makes it difficult to run these experiments, especially, on a wholesale scale like some people think they should be run. If a man dies on your hands and you are sued for $100,000 who pays that? That is one thing, and also, if he dies, who supports your relatives that need supporting? There are a lot questions of that nature that are not answered by such things as that. I think that there is always difficulty in getting volunteers.

THE CHAIRMAN: The British use a different system, don't they?They take troops and assign volunteers.

COLONEL BAYLISS: That's right. They do have a system of rewarding now. That is, they pay them so much money and it isn't any large sum of money, but they do have a system of rewarding, but we don't have such a system.

DR. WORTHLEY: Do they have all these restrictions? Are they as much concerned about the legal aspects?

COLONEL BAYLISS: I would think so. They don't run experiments that are extremely dangerous. I think we run experiments that are practically up to the same level of danger, but we don't run them inthe same large numbers and

...we do not have the volunteers coming in at all times. I don't know whether they have any greater protection, either for the volunteers or for the experimentors. I think they are about the same.

DR. WORTHLEY: This document I just read was considered by the Committee onHuman Resources at their meeting on Friday, and thereame in just a few minutes ago this communication from them on the subject. It has their reflections on this matter of the use of human volunteers, If the Committee would like it read.

THE CHAIRMAN: If it is not too long.

DR. WORTHLEY: No, it is just about a page.

All right. Here it is. The Proposed Use of Human Volunteers. "The paper under consideration was presented to a selected number of the members of the Human Resources Committee for discussion. The following analysis of the possible problems which may arise a number of recommendations were made: (a) that every consideration be given to the full exploitation of the law primates, particularly of the anthropoids, for experimentation of this sort. proper attention should be given to the needs of financial support to maintain a supply of animal subjects, particularly anthropoids, since the supply of such subjects of extreme concern in providing tools for such research in this cour

(b) that the psychologists need to know a great deal more about the necessity for using humans at all, since accidents involving humans are known to have occurred in the data available from such accidents can presumably be utilized. (c) if such experiments are conducted, psychologists would like to impose certain conditions for such experiments, particularly since the stress condition is not believed to be a true one and may well interfere with the elicitation of adequate data and information; (d) the experiments, whether animal or human, if humans are to be used, should not be or a random or similar nature, and should include, where appropriate, psychologists as members of the research group, since attitudes of general behavior of the experimental subject will be involved, and psychologists are very much concerned about such studies; (e) due consideration should be given to the maintenance of safeguards in such experiments in the event human volunteers are used, and some incorporation of a statement in policy document which would indicate (1) the Government's liability in such situations, and (2) the insurance benefits which may accrue the individual or to his family, in the event of accident or death."

THE CHAIRMAN: Well, gentlemen, what position do we want to take with respect to this Paragraph 31? I wonder

...if it would be helpful to us to have the suggestion which Colonel Bayliss would have on this. Colonel Bayliss, do you have anything that you want to suggest to us? You have this Paragraph 31 before you, do you?

COLONEL BAYLISS: Yes, sir, I am in agreement with this paragraph.

THE CHAIRMAN: You are in agreement. Well, is there anything that the Committee would care to do to it? It isn't quite in line with what -- in view of the statement we had read to us, I suppose that they are under consideration, but I suppose that's the statement that's at issue, isn't it?

DR. WORTHLEY: Yes, that's this statement here. We knew that they were considering something, but we didn't have the finished paper.

DR. AUSTIN: I think we can let this stand as it is.

THE CHAIRMAN: Is the Committee agreeable to let it stand as it is?

COLONEL CARTER: Mr. Chairman, I think that, possibly, we might add something to this underlined portion. Inasmuch as it's been indicated that these volunteers aren't protected, legally, and get no pay for it, you might add something to this effect, and provision be made for hazardous duty pay to volunteers where it is determined that this is a ppropriate.

COLONEL FENCE: According to what the Medical Policy Council put out you can't do it if there is any hazard. I mean, they state you can't do it if there's any chance

COLONEL BAYLISS: I think it might be difficult to get it through on that hazardous duty thing because you run into all these requirements that say it must not be hazardous. Well, there is a hazard in everything you do, including crossing the street, and just being any place is hazardous at times, so that I think it has to be some method other than that, and there are large numbers of groups that are trying to get this hazardous duty pay. This will be just one more among many groups that are trying to get it and all that it's going to do is to make it more difficult for those people who are already getting hazardous duty pay. It will just thrown them all out, eventually.

THE CHAIRMAN: Colonel Batlin, you had something?

COLONEL BATLIN: I'd like to take the other side to what Colonel Bayliss said. You ask a man to go into a gas chamber filled with GB without a gas mask. It's hazardous getting him to walk through that door and he is entitled, for the moral courage of walking throughthat door, for hazardous duty pay. Nobody is forcing him to do it, and it is a hazard. It's not like walking across the street.

One of the ways of getting a good supply of volunteers is to make it profitable for them to risk their lives. We have had accidents. It could happen, that before that goal was opened up again, the man got out. His life would be gone, or he might be left an invalid.

Volunteers could be encouraged very much by recompensi

COLONEL BAYLISS: I agree with what Colonel Batlin has said, except I don't know whether you would be able to get it through.

DR. JOHNSTONE: There is no harm in recommending it.

COLONEL BAYLISS: I think there is some requirement that they spend six days there out of the month, or something like that. I don't know whether they have to spend six days under experiment during the month to collect the pay or not. All those little things ought to be ironed ou Does a man get hazardous duty pay for an entire month for a single day, or does he have to be in six different experiments during the month?

DR. JOHNSTONE: I am not sure that everyone in the roo realizes the importance of this. Dr. McGee Harvey pointe out last week that we will not make progress in a lot of these toxicity studies unless we make experiments with human volunteers.

For instance, the question which is mentioned in

Percutaneous effects of GB, has come up just because the British made such experiments, and so this is a serious thing. I don't see any reason why the Committee should not make strong recommendations. The fact is, both the British and Canadians do extensive experiments with human volunteers in mass . It isn't a problem that can be solved by one or two experiments, and if we can strengthen this thing somewhat along the lines that Colonel Cather has suggested, I think it would be well worth our effort and time that we have spent on it.

COLONEL FINCKE: I wanted to determine from Colonel Cather, specifically, the mention of the word "hazardous", whether this was [portion inaudible] or submarine pay, etc., or is this another type of hazardous duty pay?

COLONEL CATHER: I had in mind some similar type of pay. However, I think it could be modified to state something as "an appropriate reward, monetary or otherwise."

DR. WORTHLEY: I have been trying to put some of these thoughts in language here, and thought of the possibility of adding a phrase "be brought to the attention of the Armed Forced Medical Policy Council, and that provision be made for a system of rewards for such volunteers and for . . . of Government liability in case of accidents to include insurance coverage."

COLONEL BAYLISS: I think that would be perfect.

THE CHAIRMAN: Is that agreeable to the Committee? I take it there is no disagreement. We can pass on.

COLONEL FINCKE: How much work has been done with anthropoids with GB? Has that been exploited to the fullest?

COLONEL BAYLISS: We used considerable numbers of monkeys, not GB chimpanzees. We haven't used chimpanzees. They are much more difficult to obtain. We could use some. We used considerable numbers of monkeys.

DR. JOHNSTONE: I might point out the Germans used chimpanzee -- apes, they call them -- in testing of GA during the war.

COLONEL BAYLISS: We'd be very glad to use them.

DR. JOHNSTONE: Is this matter of apes and monkeys something we can leave to the experts? Paragraph recommends more attention be given to chemical warfare.

COLONEL CATHER: The second paragraph in 32 is contrary to what the panel put down.

DR. JOHNSTONE: Are you referring to the psycho-chemical fields, Colonel Cather?

COLONEL CATHER: Yes, sir, CPT107/2, Page 2, Paragraph 1, "The figure has been rounded off to 100, for men at rest. It has been established in man that the same per cent of

TOP SECRET

OFFICE OF THE SECRETARY OF DEFENSE
ARMED FORCES MEDICAL POLICY COUNCIL
WASHINGTON 25, D. C.

22 October 19[illegible]

MEMORANDUM FOR D[illegible]

I discussed the attached with [illegible] on Saturday. She concurred in the conditions except that she recommended that a provision be added to 1. requiring that the consent be expressed in writing before at least one witness.

I have added such language in the appropriate place under number 1. The new matter is underlined. Mrs. [illegible] has approved this language.

Mr. Kent the General Counsel, has approved this addition from the legal standpoint.

I recommend that the conditions be so amended.

Stephen S. Jackson
Stephen S. Jackson

1 attachment

TOP SECRET [illegible]

RESEARCH AND DEVELOPMENT BOARD
WASHINGTON 25, D. C.

12 November 1952

MEMORANDUM FOR THE VICE CHAIRMAN, RDB (DR. FLOYD L. MILLER)

SUBJECT: Human Experimentation

1. At its seventeenth meeting 30-31 October, the Committee on Medical Sciences briefly discussed the problem of human experimentation. The committee agreed that before it could issue or endorse any policy statement on this subject, it would want to have the matter studied by a special ad hoc working group which would report to the committee. The committee is cognizant of the fact that human experimentation has been carried on for many years by capable investigators. To issue a policy statement on human experimentation at this time would probably do the cause more harm than good; for such a statement would have to be "watered-down" to suit the capabilities of the average investigator. Thus, it would be restrictive to the exceptional research worker.

2. Human experimentation within the field of medical sciences has, in years past, and is at present governed by an unwritten code of ethics. This code of ethics which is administered informally by fellow workers in the field is considered to be satisfactory.

3. To commit to writing a policy on human experimentation would focus unnecessary attention on the legal aspects of the subject. The legal aspects have in months past, and are currently receiving intensive study by the United States Public Health Service, which will shortly open a new Clinical Center devoted to human experimentation. One of the main issues involved in the discussion of the legal aspects is whether the human volunteer is truly a volunteer, or whether he is motivated to "volunteer" by the perquisites that he assumes, rightly or wrongly, will accrue to him as a result of volunteering.

Lloyd Mussells

F. LLOYD MUSSELLS, M.D.
Executive Director
Committee on Medical Sciences

COPIED: 7/8/94
RECORD GROUP: 330
ENTRY: 1411
FILE: RDB-HR- 278

~~TOP SECRET~~

OFFICE OF THE SECRETARY OF DEFENSE
WASHINGTON 25, D. C.

MEMORANDUM FOR DR. MELVIN A. CASBERG, M. D.

SUBJECT: The standards and requirements to be followed in human experimentation.

It is recommended that the attached principles and conditions for human experimentation, which were laid down by the Tribunal in the Nuremberg Trials, be adopted instead of those previously submitted by me, with the following change:

In No. 5 delete everything after the word "occur" and insert the period after that word.

Add (1)(g) of previously submitted conditions to wit:

"11. Whereas prisoners incarcerated in penal institutions may not give their consent if the required conditions are met, prisoners of war will not be used in human experimentation."

Stephen S. Jackson
Counsel

Attachments (3)

~~TOP SECRET~~

CCTIED: 9/26/94
RECORD GROUP: #330
ENTRY: #1999
FILE: 333 1952

HHS-072894-A

Mr. Rourke - 136, Bldg. 1, NIH

FEDERAL SECURITY AGENCY
Office of the Administrator
Office of the General Counsel

GC:FH

Dr. John A. Trautman
Director, Clinical Center

December 5, 1952

Mr. Edward J. Rourke
Legal Adviser, NIH
Office of General Counsel
Research - Clinical Investigations - Administrative Methods to Assure Patient Participation on Fully Informed and Voluntary Basis

At your invitation, I presented to the Medical Board of the Clinical Center on December 2 a proposal that, in view of several factors in some degree peculiar to the Clinical Center, it would be advisable from the legal point of view among others to accept certain procedures relating to patient admission that are more formal than might otherwise be considered necessary. It was thus proposed in particular to secure from patients as a uniform practice a written statement, signed preferably before admission, indicating the patient's awareness and acceptance of the nature of the particular investigation in which he was to participate and acceptance of any particular inconvenience or risk inherent in his participation. I offered to prepare, for further consideration by the several Institutes, samples of such a statement drafted to cover projects that the Institutes plan for early activation.

I think it fair to say that of the members of the Medical Board that expressed their views, and most did so, all rejected such a proposal. The rejection was one, as I understand it, not to any particular detail but rather a more basic objection to written, as compared to oral, statements. There was apparently, therefore, no objection to providing the patient with enough information to permit him to exercise an informed choice of participation or refusal as long as not reduced to writing for his signature.

I will not burden you here with repetition of the factors that in my judgment make it advisable to use statements subscribed by the patient. I note only that the reasons for the use of "consent" forms for standard surgical procedures, a practice your Board apparently accepts, apply in my opinion with greater force to clinical investigations. On the other hand, the methods to be used to assure that patient participation is on an informed and voluntary basis are matters of administrative choice, since no pertinent law precludes the National Institutes of Health from undertaking either the risks of liability arising from use of oral rather than written evidence, or the risks to effective administration arising from the use of other than the best record to demonstrate that a policy of proceeding only on the basis of informed consent has been carried out. I would like to suggest, however, that whatever be the decision, the matter is of such importance to the NIH from the point of view of legal liability that Mr. Sebrell be at least informed.

Members of the Medical Board did discuss the possibility that special occasions would arise when it would be advisable to have a statement signed by the patient. It is not yet clear what the criteria would be on the basis for which such situations would be identified. The discussion suggested that one of them would be where harmful consequences to the patient could not be excluded in advance with assurance. It may be that you will want to secure a degree of uniformity in Clinical Center administration by developing criteria, acceptable to the Institutes, for identifying such situations so that special precautions can then be used. If so, I would be glad to work with any officer or group you may designate for this purpose.

In view of the Medical Board's basic reaction to my initial proposal and its apparent preference for a selective approach, I suggest that it would serve no useful purpose to undertake at this time a draft of sample statements appropriate for general use upon patient admission. I would be glad, of course, to assist any project director if it be decided that his project is of such nature that a statement signed by the patient is advisable.

A copy of this memorandum is being forwarded to Dr. Wilder for his information in his capacity as Chairman of the Committee on Principles Governing Clinical Research.

Edward J. Bourbe

APPENDIX II

M E D I C A L R E A R C H P R O G R A M S
O F T H E
V E T E R A N S A D M I N I S T R A T I O N

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GEORGE M. LYON, M. D.

ASSISTANT CHIEF MEDICAL DIRECTOR

for

RESEARCH AND EDUCATION

Prepared for:

Committee on Veterans Medical Problems
National Research Council

8 December 1952

The results of the research activities of the investigators are published in the professional, scientific, and technical journals so that information so derived can be made available not only to other VA personnel but to the interested professions as well. In this manner the public, at large, may benefit from the research achievements within the VA Research Program. A surprisingly large number of these publications indicate a joint authorship in which one of the authors is a full-time employee of the Veterans Administration and the other is a member of the faculty of the medical school or university associated with the VA hospital. This is but one of the many evidences of a community of interest that contributes so much to the Medical Program of the Veterans Administration.

There have, unfortunately, been times when some of our associates have been a bit neglectful of giving us proper credit for work they have done in close association with our research workers. While we are not pleased when this occurs we do have the satisfaction of knowing that we have contributed to their success through our cooperation and participation and that they have inadvertently paid us a compliment, even though not widely advertised, by thinking so highly of our contribution that they would like to "hog" the credit for it to themselves.

In general, we encounter much the same problems of human relations that characterize comparable situations within medical schools and university hospitals. Fortunately, we do have a minimum number of instances wherein a senior person may try to get his name on all publications within his service (in a medical service or department), regardless of the validity of his contribution thereto. The Research Committees serve an important and beneficial influence in moderating these abuses which, if not moderated, can have a most disturbing influence on the attitudes and the morale of the other research workers. I mention this only to point out that we are concerned with many of the same problems with which deans of medical schools and heads of departments in universities are concerned. Sometimes these problems can be most disconcerting to the responsible research administrator. Within the VA Medical Research Program we are rather fortunate because there has been displayed, as a general rule, an exemplary spirit of fairness and sportsmanship-like attitudes in such matters.

PART II

VA RADIOISOTOPE PROGRAM

HISTORICAL

During the Fall of 1946 and the Spring of 1947, General Paul Hawley, who was then Chief Medical Director, became deeply concerned about the problems that atomic energy might create for the Veterans Administration due to the fact that the Armed Services were so actively engaged in matters of atomic energy. After consultation with the representatives of the Manhattan Engineer District, General Hawley convened a conference within his office to consider this matter. The conference, held on August 7, 1947, was attended by Lieutenant General Leslie R. Groves, USA, Commanding General, Manhattan Engineer District; Colonel James Cooney, MC, USA, Chief Medical Officer, Manhattan Engineer District,; Major General Raymond Bliss, USA, Surgeon General, U. S. Army; Rear Admiral W. L. Willcutts, MC, USN, Deputy Surgeon General, US Navy; Major General Malcom Grow, Air Surgeon, U.S.A.F.,; Surgeon General Leonard Scheele, U. S. Public Health Service; General Hawley and myself. General Groves described, in general,

characteristics that these problems might include and then stressed the importance of having personnel trained, qualified and equipped with the facilities required to meet them.

General Hawley then requested Doctors Stafford Warren, Hymer L. Friedell, Shields Warren, Hugh Morgan, and Perrin Long to constitute a committee to advise him on matters of atomic medicine and to make recommendations as to what steps should next be taken to meet the problems discussed at the August 7th conference.

On September 5, 1947, this committee held its first meeting. The Veterans Administration was represented by General Hawley and myself. At this time the objectives of the Atomic Medicine Program were formulated and the broad aspects of a scheme for establishing a radioisotope program to support the more inclusive Atomic Medicine Program were drafted. The advisory committee was given the name, "Central Advisory Committee on Radioisotopes", as it was not desired at this time to publicize the fact that the Veterans Administration might have any problems in connection with atomic medicine especially the fact that there might be problems in connection with alleged service-connected disability claims. The committee recommended, (a) the establishment of an Atomic Medicine Division within the Department of Medicine and Surgery and the appointment of a Special Assistant for Atomic Medicine to head up the Division and to represent the Chief Medical Director in the handling of atomic medicine matters, and (b) the establishment of a Radioisotope Section to implement a Radioisotope Program. It further recommended that, for the time being, the existence of an Atomic Medicine Division be classified as "confidential" and that publicity be given instead to the existence of a Radioisotope Program administered through the Radioisotope Section. General Hawley took affirmative actions on these recommendations and it was in the manner described that the Radioisotope Program was initiated in the Fall of 1947.

The unique qualifications of the members of the Central Advisory Committee on Radioisotopes merit consideration. Doctor Stafford Warren, now Dean, Medical School, University of California, Los Angeles, was formerly Chief Medical Officer, Manhattan Engineer District (1943-1946). Doctor Hymer Friedell, now Professor of Radiology, Western Reserve Medical School, was Deputy Chief Medical Officer, Manhattan Engineer District (1943-1946). Doctor Shields Warren, now Professor of Pathology, Harvard Medical School, was Director, Division of Medicine and Biology, Atomic Energy Commission (1947-1952). Each of these individuals had participated in one or more atomic bomb tests in positions of senior responsibility. Doctors Morgan and Long have, for many years, been leaders not only in academic and civilian medicine but in military medicine as well.

The Radioisotope Program was initiated in the Fall of 1947. Most of that Fall was spent in planning. The first radioisotope laboratory was opened at VA Hospital, Van Nuys, Calif., in February, 1948, under the direction of Dr. M. E. Morton, one of the pioneers in research with radioisotopes at the University of California. This was but a few months after radioisotopes became generally available for medical purposes by the Atomic Energy Commission.

GENERAL STATEMENT OF OBJECTIVES AND PRINCIPLES

A major objective of the Radioisotope Program was, from the very beginning, to provide the Veterans Administration with qualified professional, scientific, and technical personnel, as well as the specialized facilities, required, (a) to meet the varied and unique problems of atomic energy that

might be of concern to the Veterans Administration, particularly in respect to the problems associated with the study and analysis of alleged service-connected disability claims, and (b) in connection with certain responsibilities that the Veterans Administration may have in civil defense. Much of the support for the Radioisotope Program has been predicated on, and justified by, the implications of this major objective. In this respect, it differs somewhat from other activities carried on within the VA Medical Research Program and supported from research funds (Program 8200).

The specific objective of the Radioisotope Program has been, and is, to employ radioisotopes within selected hospitals of the Veterans Administration, (a) in medical research, (b) in clinical diagnosis, and (c) in the medical treatment of veteran patients. Here again the Radioisotope Program differs somewhat from other activities supported from research funds in that it includes activities involving clinical diagnosis and treatment as well as research. As a matter of fact, in the larger and more active Radioisotope Units perhaps as much as one-half of their energies are expended in clinical diagnosis and treatment, particularly the former.

Radioisotope laboratories are established only in VA hospitals having affiliation with medical schools.

The Atomic Energy Commission has established certain criteria and standards of health protection, not only for the patients receiving radioisotopes, but as well for individuals who work with, or might be inadvertently exposed to, radioisotopes. These requirements are strictly observed within the VA Radioisotope Program.

The Veterans Administration, for reasons unique to its needs and responsibilities, has established certain requirements, both technical and administrative, which are rigorously observed within the Radioisotope Program.

Certain policies recommended by the Central Advisory Committee on Radioisotopes and established by the Chief Medical Director have been established and compliance therewith is a firm requirement within all VA hospitals where radioisotopes are employed. These include:

a. medically sound policies and practices with respect to all human applications of radioisotopes

b. sound policies and practices with respect to radiological safety, including appropriate technical and administrative requirements and a radiological safety plan formally drawn up and approved by the Radioisotope Committee and the Chief, Radioisotope Section

c. sound, conservative policies and practices with respect to both publicity and public relations,

d. supervision of the radioisotope program within an individual VA hospital by a Radioisotope Committee representing the Deans Committee affiliated with that hospital.

As a statement of principle, it is maintained that a conservative stand should be taken with respect to the position of radioisotopes in medicine within all VA hospitals in which radioisotopes are employed. This is particularly true in respect to treatment. The situation is very much more encouraging in clinical diagnosis where we have reason for greater optimism. It is generally believed, however, that the main contribution that radioisotopes can make to medical care will be as a tool in biological and medical research.

Within the VA Radioisotope Program, radioisotopes may be, and are, employed in basic research as well as in medical research and clinical investigations.

The Radioisotope Program complements but does not duplicate, or take the place of, the program conducted by the Atomic Energy Commission. This agency has no means whereby it could provide either the research or clinical services involving the use of radioisotopes that are required within the Veterans Administration, nor does any other agency of government. . . .

The Radioisotope Program, as an integral part of the over-all Medical Research Program of the Veterans Administration, augments and extends the accomplishments of the research program within VA hospitals. It is closely integrated with the medical research programs within these hospitals. Insofar as practicable, radioisotope laboratories have been placed in close proximity to the medical research laboratories within an individual hospital.

Because of the unique requirements associated with the employment of radioisotopes within hospitals, particularly in a large hospital program such as that of the Veterans Administration, a much greater degree of central control is needed than is required in the other medical research or clinical investigation programs.

Radioisotopes may be used only in VA hospitals for which the Chief Medical Director, upon recommendation of the Central Advisory Committee on Radioisotopes, has specifically authorized the establishment of a Radioisotope Unit.

Within a VA hospital in which there has been established a radioisotope unit, there is freedom of use of radioisotopes provided, (a) applicable requirements of the Atomic Energy Commission and of the Veterans Administration are observed, and (b) such use has previously been approved by the Radioisotope Committee appointed to represent the Deans Committee in the supervision of the Radioisotope Program within that particular VA hospital.

In general, the same policies and principles pertaining to the Medical Research Program, as described earlier in this presentation, are applicable to research involving the use of radioisotopes.

During the first four years of the program, representatives of all VA radioisotope units met twice yearly in a working conference intended to provide exchange of information concerning, (a) administrative matters, (b) scientific and technical matters unique to the employment of radioisotopes, (c) the planning, organization, and conduct of research with radioisotopes, and (d) the results of research work and clinical investigations in which radioisotopes were used.

ORGANIZATION AND ADMINISTRATION WITHIN CENTRAL OFFICE

GENERAL STATMENT

The Special Assistant for Atomic Medicine serves as Chief, Atomic Medicine Division. He is responsible for the over-all administration of the VA Radioisotope Program and for its coordination within the professional services.

RADIOISOTOPE SECTION

The Radioisotope Program is administered through the Radioisotope Section, Atomic Medicine Division, Research and Education Service. The Chief, Radioisotope Section, is responsible for the coordination within Central Office of those matters with which the administrative divisions within a VA hospital are concerned.

The Radioisotope Section is assisted, both in an advisory capacity and in a service capacity, by the Central Advisory Committee on Radioisotopes. The members of this Committee serve as consultants to the Radioisotope Section. Three members also serve as special consultants to the hospital programs within certain regions. These are, (a) Eastern United States, Dr. Shields Warren, (b) Central United States, Dr. Hymer Fridell; and (c) Western United States, Dr. Stafford Warren. Obligations incurred in connection with these services, and those of other special consultants in atomic medicine, amount to $10,000 annually.

The Radioisotope Section provides assistance and support to the Radioisotope Units, (a) in professional, scientific, and technical matters, (b) in administrative matters (personnel, finance, budget, supplies, and equipment, construction, etc.), (c) in program analysis, (d) in dissemination of information gained from semi-annual progress reports submitted by the Radioisotope Units, (e) in serving as a medium for exchange of information, and (f) in providing a wide variety of advisory services.

To assist the VA hospital in initiating and administering a radioisotope program, certain aids have been prepared by the Radioisotope Section and are provided to the Deans Committee and the Manager of the hospital concerned. These include, (a) "Suggestions for Planning and Initiating a Radioisotope Program within a VA Hospital", (b) "Suggestions as to Plan of Organization and Operational Procedures of a Radioisotope Unit within a VA Hospital", (c) "Suggestions as to Supply and Equipment Operations for a Radioisotope Unit", and (d) "List of Initial Supplies and Equipment for Radioisotope Units". These have proven to be most helpful to those concerned with the development and administration of the radioisotope programs within the VA hospitals having radioisotope units.

The Radioisotope Section has also planned, organized, and administered a program designed to train VA personnel to serve as monitors and monitor leaders in the radiological safety aspects of civil defense. To accomplish this, in the summer of 1949, the section also prepared for, and provided to, the VA hospitals a training guide under title, "Training Plan for Course in Radiological Defense (Monitors)". By the summer of 1950 within VA hospitals having Radioisotope Units more than 400 VA employees, other than physicians, dentists, and nurses, had received the training.

The Radioisotope Section, in 1950, cooperated with the Federal Civil Defense Administration in the preparation of "Health Services and Special Weapons Defense" (AG-11-1).

The Radioisotope Section, in 1951, assisted in the preparation of two manuscripts which were reproduced and widely distributed by the Council on National Emergency Medical Services of the American Medical Association. They were: "Planning and Organizing for Radiological Defense in Civil Defense", and, "Training Plan for Courses in, (a) Medical Aspects of Radiological Defense, (b) Medical Aspects of Atomic Warfare, and (c) Radiological Defense (Monitors)". These were modifications of manuscripts already prepared for use within the Veterans Administration.

RADIOISOTOPE UNIT

The organizational element within the VA hospital concerned with the use of radioisotopes is the Radioisotope Unit. It is under the immediate supervision of a director who is a physician qualified in the use of radioisotopes as well as in the field of clinical medicine and medical research. The director is appointed with the approval of the Chief Medical Director.

The director is assisted in an advisory and a supervisory capacity by the Radioisotope Committee representing the Deans Committee of the hospital. The duties of this committee are:

a. advise the Manager as to policy in regard to radiological safety, public information, and public relations

b. make recommendations as to the qualifications, appointment and employment of professional, scientific, and technical personnel required in the unit, including the director and all consultants to the unit

c. review and, if approved, recommend proposed research activities involving radioisotopes, and proposed clinical uses of radioisotopes, and

d. review, and when appropriate, approve, (1) such papers as may be proposed for publication, and (2) such exhibits as may be proposed for presentation before scientific groups when either involves the use of radioisotopes.

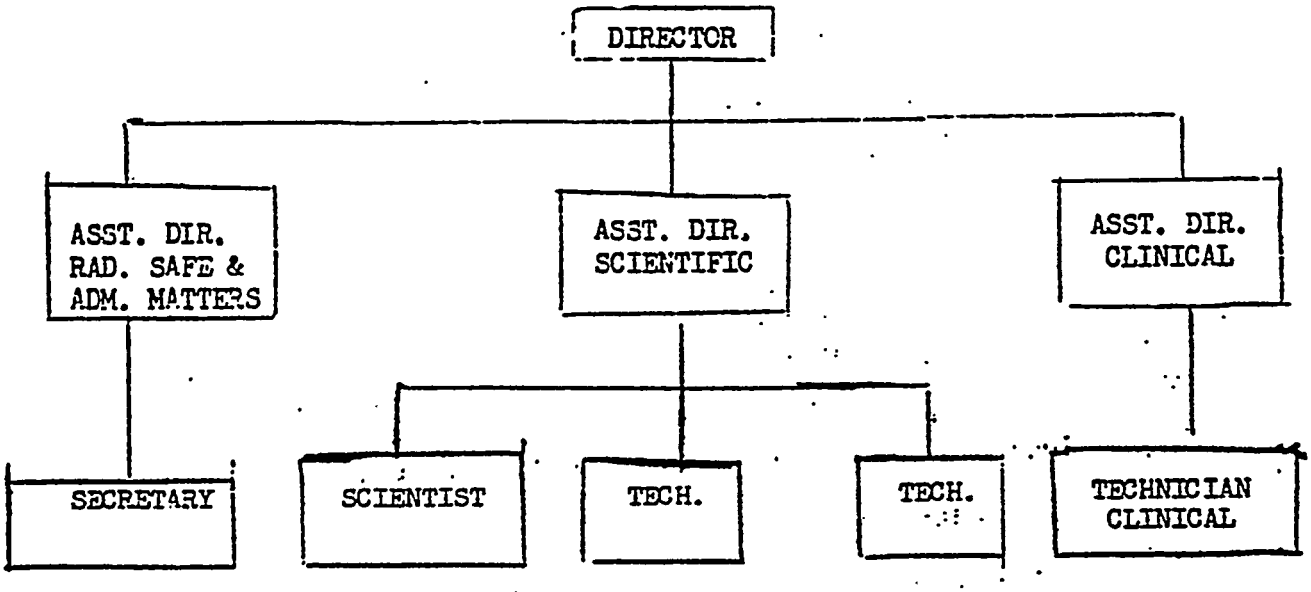
Membership on the Radioisotope Committee is not limited to members of the Deans Committee. Members may not be full-time employees of the Veterans Administration. Usually the members are qualified individuals within the teaching staff of the associated medical schools or universities.

Consultants may be professional, scientific, or technical personnel and need not necessarily be physicians.

Within the VA hospital and laboratories, the director is responsible, (a) for the administration of the Radioisotope Program, (b) for the human application of radioisotopes, and (c) for all radiological safety measures.

The Director is assisted by three principal assistants as indicated in the accompanying organization chart.

As a rule, the Radioisotope Unit is organized in this manner:



The Director and the Assistant Director (Clinical are physicians employed under Department of Medicine and Surgery. They are not paid from research funds (Program 8200). The others are employed under regulations of the Civil Service Commission. They are paid from Research funds (Program 8200). Only citizens of the United States may be employed in any of these positions.

Of funds made available for the Radioisotope Units, 80 per cent is utilized for the payment of salaries of the scientists and technical personnel, other than physicians, dentists, and nurses, 5 per cent for consultants and 15 per cent for supplies and equipment.

SCOPE

The scope of the Radioisotope Program includes:

a. Employment of radioisotopes in medical research in a great variety of applications in the broad field of medical research. Special attention has been given to study of (a) thyroid function, (b) diseases, and disorders of the thyroid gland, (c) metabolism, (d) cardiac function, (e) peripheral vascular disease, (f) electrolyte balances, (g) blood volume determinations, (h) hemodynamics of cardiovascular system, and (i) etc.

b. Clinical diagnostic procedures have been developed and are employed in a variety of conditions including (a) practical diagnosis of hyperthyroidism and hypothyroidism, (b) the location and diagnosis of metastatic carcinoma of the thyroid, (c) diagnosis and localization of brain tumors, (d) determining pumping efficiency of the heart, (e) peripheral vascular function, (f) blood volume determinations, and (g) skin grafts, etc.

c. Treatment of (a) toxic hyperthyroidism, (b) carcinoma of thyroid and metastases, (c) leukemia, (d) polycythemia vera, (e) carcinoma of the testicle, (f) carcinoma of the prostate, (g) certain tumors (by interstitial infiltration), and (h) basal cell carcinoma of the skin.

OUTSTANDING ACHIEVEMENT

Outstanding technical achievements have been (a) the application of scintillation counters in clinical diagnosis and treatment as well as in medical research, (b) the application of the Texas well counter to medical research uses and (c) the development of the automatic "scanner" for making "scintigram" tracings of the outline of the thyroid gland and of brain tumors.

PART III

VA PROSTHETICS AND SENSORY AIDS RESEARCH PROGRAM

INTRODUCTION

Faced with considerable numbers of individuals who had suffered amputations in active service during World War II, the War Department turned to the National Research Council for assistance in the rehabilitation problems of these individuals. There was established then in 1947 through the National Research Council, a Committee on Artificial Limbs, supported first by the Office of the Surgeon General and later the Veterans Administration, to outline a continuing program of research and development in this field.

The purpose of this program has been to develop improved prosthetic and orthopedic appliances and sensory aids, exclusive of dental prostheses, and includes the practical utilization of these devices by veteran patients. The aim of the program is to conduct research and development of new and improved prosthetic and orthopedic appliances and sensory aids and to afford an opportunity for the testing and fitting of these devices so that the problems of successful utilization may be understood and surmounted. There exists a large number of disabled beneficiaries (most recent estimate - 257,500) who, under federal statutes, will remain permanently entitled to prosthetic and sensory aids and unless the Veterans Administration conducts an active prosthetics research and development program in this field, the interest of veteran individuals who are handicapped and disabled will not be served to the best advantage.

AUTHORITY

Public Law 729, 80th Congress, gives specific authorization for the Prosthetic and Sensory Aids Research Program, and authorizes the appropriation of up to $1,000,000 annually for this purpose.

ORGANIZATION AND ADMINISTRATION

The Prosthetic Research Program is coordinated with other Veterans Administration medical research and is administered as to financial and contractual matters by the Assistant Chief Medical Director for Research and Education. The program is developed, planned, and supervised, however, by the Director, Prosthetic and Sensory Aids Service, Central Office.

NATIONAL ACADEMY OF SCIENCES-NATIONAL RESEARCH COUNCIL

Division of Medical Sciences

MINUTES OF THE COMMITTEE ON VETERANS MEDICAL PROBLEMS

29th Meeting - 20 April 1954

ATTENDANCE:

Committee:	Dr. Wilburt C. Davison, Chairman Drs. J. E. Finesinger, A. McGehee Harvey, Esmond R. Long, Perrin H. Long, Herbert H. Marks, and H. Houston Merritt. Absent: Drs. M. E. DeBakey, A. LeRoy Johnson, Donald Mainland, and J. Roscoe Miller.
Veterans Administration:	Drs. George M. Lyon, Martin Cummings, Theodore S. Moise, Robert E. Stewart, and Augustus Thorndyke.
U. S. Army:	Dr. Ardie Lubin, Psychology Department, Army Medical Service Graduate School, Walter Reed Hospital.
Selective Service System:	Lt. Col. Clark Young.
Bio-Sciences Information Exchange:	Drs. Stella Deignan and Harley N. Gould.
National Research Council	Drs. R. Keith Cannan, Philip S. Owen, G. W. Beebe, Thomas Bradley, B. M. Cohen, J. O. Cole, Seymour Jablon, Edgar M. Neptune, Jr., and L. H. Warren.

The meeting was called to order at 10:00 a.m. by the chairman, Dr. Wilburt C. Davison.

I. Consideration of the Minutes of the Previous Meeting

The minutes of the previous meeting were approved without change.

II. Some Results of the Artificial Limb Program

Dr. Augustus Thorndyke, Acting Director, Prosthetics and Sensory Aids Service of the Veterans Administration, briefly described the VA prosthetics research program. (See Appendix I.) Dr. Thorndyke mentioned that the work is primarily contractual but that the devices are evaluated in 30 VA centers by orthopedic and prosthetic appliance teams. This talk was illustrated by a display case containing old and new upper-extremity prostheses. Two amputees demonstrated upper- and lower-extremity prostheses. The upper-extremity, above-elbow prosthetic was manipulated by a plastic hook attached to a grafted pectoralis major muscle tunnel. This muscle, according to the demonstrator, is capable of developing a maximum power of 100 pounds.

[Appendix to Minutes of Meeting of CVMP 4/20/54]

APPENDIX VII

TABULATED SUMMARY FROM ANNUAL PROGRESS REPORTS OF RADIOISOTOPE UNITS

On December 31, 1953, there were 33 Radioisotope Units either established or in process of activation. Of these 22 were actually using radioisotopes to varying degrees. The others were procuring equipment and personnel and several have received their first allocations of radioisotopes since January 1, 1954.

On duty in the Units at the end of 1953 were:

Full time physicians, under DM&S	29
Full time Civil Service employees	173
Residents assigned for part time	17
Consultants rendering services	65
Others (on grants, etc.)	11

The work of the Units may be summarized under three headings, with summarized totals which are approximate:

1. RESEARCH

Active research studies under way	211
Articles published in journals during year	85
Articles accepted for publication later	51
Lectures and other presentations to groups other than VA staff meetings	169

2. DIAGNOSIS EMPLOYING RADIOISOTOPES

Thyroid uptake studies, varying techniques & times	6279	studies, 4551 patients
Thyroid clearance studies	699	
Thyroid scanning procedures	788	
Protein-bound iodine determinations	1055	
Thyroxine synthesis rate determinations	443	
Blood volume determinations using human serum albumin, or P-32	457	
using Cr-51, (red cell volume)	537	
Radiocardiographs	4	
Circulation time studies	109	
Peripheral vascular studies	208	
Studies using Fe-59 (red cell survival, etc.)	167	
Brain tumor localization	180	
Scanning for liver metastases, pyelograms, etc.	129	
Miscellaneous diagnostic procedures	1812	

3. THERAPY USING RADIOISOTOPES

	62 doses to	48 patients
Polycythemia vera	111	42
Chronic leukemia (lymphatic or myelogenous)	89	25
Thyroid carcinoma	329	271
Hyperthyroidism	50	32
Thyroid ablation for cardiac disease	19	19
Prostate carcinoma	46	42
Pleural effusion by radiogold colloid	18	13
" " " chromic radiophosphate	16	11
" " " Yttrium-90 colloids	5	5
Radiogold interstitially	74	74
Chromic radiophosphate interstitially	25	
Miscellaneous therapeutic procedures		

SECRETARY OF DEFENSE ROUTING SLIP (Classified)

CLASSIFICATION: TOP SECRET

SECURITY INFORMATION

FROM: The Secretary of Defense

	TO	INITIAL		TO	INITIAL
	THE DEPUTY SECRETARY OF DEFENSE			ASSISTANT TO THE SECRETARY OF DEFENSE (ISA)	
	DIRECTOR, EXECUTIVE OFFICE OF THE SECRETARY			DIRECTOR, OFFICE OF FOREIGN MILITARY AFFAIRS	
	DEPUTY DIRECTOR, EXECUTIVE OFFICE OF THE SEC.			DIRECTOR, OFFICE OF MILITARY ASSISTANCE	
	SECRETARY OF ARMY			DIRECTOR, NORTH ATLANTIC TREATY AFFAIRS	
	SECRETARY OF NAVY			DIRECTOR, OFFICE OF PSYCHOLOGICAL POLICY	
	SECRETARY OF AIR FORCE				
	ASSISTANT SECRETARY OF DEFENSE (Compt)		2	CHAIRMAN, ARMED FORCES MEDICAL POLICY COUNCIL	
	ASSISTANT SECRETARY OF DEFENSE (M & P)			CHAIRMAN, DEFENSE MANAGEMENT COMMITTEE	
	ASSISTANT SECRETARY OF DEFENSE (L & LA)			DIRECTOR, OFFICE OF PUBLIC INFORMATION	
	CHAIRMAN, JOINT CHIEFS OF STAFF			DIRECTOR, MILITARY TRAFFIC SERVICE	
	JOINT CHIEFS OF STAFF			DIRECTOR OF ADMINISTRATION	
	CHAIRMAN, MUNITIONS BOARD			DIRECTOR, OFFICE OF GUIDED MISSILES	
	CHAIRMAN, RESEARCH AND DEVELOPMENT BOARD		1	Special Security Programs	
	CHAIRMAN, MILITARY LIAISON COMMITTEE – A.E.C.				

	FOR		FOR
	PREPARATION OF REPLY FOR SECRETARY OF DEFENSE SIGNATURE	2	INFORMATION AND RETENTION
1	APPROPRIATE ACTION		INFORMATION AND RETURN FOR SECRETARY OF DEFENSE FILES
	PLEASE REPLY DIRECT FOR SEC. OF DEFENSE (Copy of reply to be forwarded to Sec. of Defense Files)		COMMENT AND/OR RECOMMENDATION
	PLEASE FURNISH DATA ON WHICH TO BASE A REPLY		NOTE AND FORWARD

FROM: Exec Sec, Committee on CW, R&D Bd

DATE RECEIVED: 9 Dec 52

TO: Special Security Programs

NUMBER COPIES: ORIGINAL: 1 (Cy No.1) | CARBON: 1 (Cy #2) | OTHER:

DATE: 9 Dec 52

SHORT TITLE: Memo — Log No. 53006

SUBJECT: Use of Human Volunteers in Experimental Research

INCLOSURES RECEIVED: 1 – Cy of CW 107/17 (Log No. 52-3059 Cy No. 11

COMMENT: 1 cc w/o Incl Distr 14 Dec 55

DUE IN CORRESPONDENCE CONTROL SECTION, EXECUTIVE OFFICE, OSD: None DEB

CONTROL NUMBER: 01593

SD FORM 1 APR 52 32 PREVIOUS EDITIONS OF THIS FORM ARE OBSOLETE

See reverse side of this form for instructions on handling attached material.

CLASSIFICATION: TOP SECRET

SECURITY INFORMATION

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DATE 3			DATE 4	01593
RECEIVED	CONTROL NUMBER			
DATE 18390				

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ENTRY: #199
FILE: 335 1952

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RESEARCH AND DEVELOPMENT BOARD
WASHINGTON 25, D. C.
COMMITTEE ON CHEMICAL WARFARE

Log No. 53006
Copy No. 1

9 December 1952

MEMORANDUM FOR THE DIRECTOR OF ADMINISTRATION, OSD

ATTENTION: Assistant for Special Security Programs,
Lt. Col. F. B. Mitman

SUBJECT: Use of Human Volunteers in Experimental Research

ATTACHED: CW 107/17, 13 November 1952

1. The TS memorandum prepared for the Secretaries of the military departments, a copy of which was submitted to this office for comment, promulgates the recommendations of the Armed Forces Medical Policy Council. These were read to the Committee on Chemical Warfare at its meeting on 10 November 1952. A Committee recommendation on this question, developed independently of the AFMPC document, was reported to the Chairman, RDB, in CW 107/17. This goes a step or two beyond the AFMPC recommendation in calling for a system of rewards for volunteers, and for recognition of government liability in case of accident.

2. The whole need of the CW program for human volunteers, in the judgment of this Committee, cannot be met by an arrangement that allows acceptance of volunteers from personnel normally on duty at installations engaged in such research. For this purpose the permissive statement should be subject to the interpretation that uniformed volunteers could be assigned to temporary duty at the experimental installation for the purpose of engaging in the program as test subjects. This is the essence of the British system, which we are advised has worked quite well.

3. It is assumed that the question has been carefully considered whether this subject should be treated in a memorandum of this nature or in one for the files, to be divulged only to those agencies and individuals who are in need of this guidance.

H. N. Worthley
H. N. WORTHLEY
Executive Director

0515

OFFICE OF THE SECRETARY OF DEFENSE
ARMED FORCES MEDICAL POLICY COUNCIL
WASHINGTON 25, D. C.

DEC 24 1952

MEMORANDUM FOR THE SECRETARY OF DEFENSE

SUBJECT: Use of Human Volunteers in Experimental Research

1. The Armed Forces Medical Policy Council has considered this subject at great length. On 17 December 1951 the Council went on record as endorsing the principle that final realistic evaluation of biological warfare must await appropriate field trials in which human subjects were used.

2. The Chemical Corps of the Department of the Army has the primary responsibility for biological warfare research, for the development of offensive strategy, tactics and weapons and for coordinating the work required to establish appropriate defense practices, methods and equipment. The medical department has not been directly involved to date.

3. At the 8 September 1952 meeting of the Council, Colonel T. F. Whayne, Chief of Preventive Medicine, Office of the Surgeon General of the Army, presented the problem of participation of the medical services in biological warfare research for the purpose of developing defense measures and devices. It was pointed out that the research had reached a point beyond which essential data could not be obtained unless human volunteers were utilized for such experimentation. This was thought to be necessary in order to arrive at a final realistic evaluation of defensive measures to be adopted for protection against the potential use of these agents as weapons in an attack on the United States. Following detailed discussion, it was unanimously agreed that the use of human volunteers in this type of research be approved. Certain limitations were placed on the use of volunteers and the manner of conducting the experiments to assure that they would be in accordance with the highest scientific requirements.

4. The Armed Forces Medical Policy Council again considered the subject at their meeting on 15 October 1952, in view of certain changes in the conditions under which experiments were to be conducted. It was resolved that the ten rules promulgated at the Nuremberg Trials be adopted as the guiding principles to be followed. An eleventh rule was added by the legal advisor to the Council, Mr. Stephen S. Jackson.

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Date 26 Dec. 1952

Recommendations: In view of previous recommendations of the Medical Policy Council that human subjects be employed as the only feasible means for the realistic evaluation and/or development of effective preventive measures of defense against atomic, biological or chemical agents, the Council further recommends that the following policy be affirmed, with respect to the participation of personnel of the Armed Services in the atomic, biological and chemical warfare research programs;

I - By reason of the basic medical responsibility in connection with the development of defenses of all types against atomic, biological and/or chemical warfare agents, Armed Services personnel and/or civilians on duty at installations engaged in such research shall be permitted to actively participate in all phases of the program. Such participation shall be subject to the following conditions:

1. The voluntary consent of the human subject is absolutely essential.

This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, overreaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision. This latter element requires that before the acceptance of an affirmative decision by the experimental subject there should be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonably to be expected; and the effects upon his health or person which may possibly come from his participation in the experiment.

The consent of the human subject shall be in writing, his signature shall be affixed to a written instrument setting forth substantially the aforementioned requirements and shall be signed in the presence of at least one witness who shall attest to such signature in writing.

The duty and responsibility for ascertaining the quality of the consent rests upon each individual who initiates, directs or engages in the experiment. It is a personal duty and responsibility which may not be delegated to another with impunity.

2. The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature.

3. The experiment should be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problem under study that the anticipated results will justify the performance of the experiment.

4. The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury.

[redacted]

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FILE: 333 1952

#12
From: L. Brownlee
Date: 11 Dec. 1952

6. Although the primary stimulus in this project originated in connection with biological warfare research, it is desired to point out that defensive measures against atomic and chemical warfare agents are equally important. For this reason all three types of agents are to be included in further experimental research.

6. The above recommendations have been coordinated with:

Mr. Stephen S. Jackson (Tabs 2, 2a and 3)
Mrs. Anna M. Rosenberg (Tab 3)
Research and Development Board, OSD, (Tab 4)

7. It is strongly recommended that a policy be established for use of human volunteers in experimental research under the conditions approved by the Armed Forces Medical Policy Council and set forth in Tab 1. Memoranda for the secretaries of the Army, Navy and Air Force covering the conditions of this policy are attached hereto for your signature, upon final approval of the policy.

Melvin A. Casberg M.D.
Melvin A. Casberg, M. D.
Chairman

Attachments - 5

Further coord: MLC
Dir Adm
Joint Staff

1 of 1 Copies

RESEARCH AND DEVELOPMENT BOA[illegible]
Washington 25, D. C.

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SECURITY INFORMATION

Log 52980
Copy 2

RDB 107/13

MEMORANDUM FOR CHAIRMAN, ARMED FORCES MEDICAL POLCIY COUNCIL

SUBJECT: Use of H Volunteers in Experimental Research

Signed FLOYD L. MILLER
FLOYD L. MILLER
Vice Chairman

Filed with Routing Slip # 01359 dtd 17 Nov 52

SECURITY INFORMATION ~~TOP SECRET~~ 01359

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FILE: 385 1952

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OFFICE OF THE SECRETARY OF DEFENSE
ARMED FORCES MEDICAL POLICY COUNCIL
WASHINGTON 25, D. C.

22 October 1952

MEMORANDUM FOR DR. CALBERG

I discussed the attached with Mrs. Rosenberg on Saturday. She concurred in the conditions except that she recommended that a provision be added to 1. requiring that the consent be expressed in writing before at least one witness.

I have added such language in the appropriate place under number 1. The new matter is underlined. Mrs. Rosenberg has approved this language.

Mr. Kent the General Counsel, has approved this addition from the legal standpoint.

I recommend that the memo will now be approved.

Stephen S. Jackson
Stephen S. Jackson

[redacted]

1 Attachment

~~TOP SECRET~~ RE TK 01466

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ENTRY: #199
FILE: 355 1952

~~TOP SECRET~~

OFFICE OF THE SECRETARY OF DEFENSE
ARMED FORCES MEDICAL POLICY COUNCIL
WASHINGTON 25, D. C.

4 December 1952

MEMORANDUM FOR MELVIN A. CASBERG, MD.

SUBJECT: The Standards and Requirements to be Followed in Human Experimentation

At a conference today with Lt. Col. F. E. Mitman, Jr., and T. C. Bedwell, Jr., it was brought out that the present wording of the subject memo in paragraph 11 has given rise to some question of interpretation of the first clause in this paragraph, to wit: "Whereas prisoners incercerated in penal institutions may and have been used if the required conditions are met". It was decided, therefore, to delete this part of paragraph 11. It was recommended, therefore, that paragraph 11 now read as follows:

11. Prisoners of war will not be used in human experimentation.

Stephen E. Jackson
Stephen E. Jackson
Counsel
Armed Forces Medical Policy Council

~~TOP SECRET~~

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RECORD GROUP: #330
ENTRY: #199
FILE: 385 1952

~~TOP SECRET~~

OFFICE OF THE SECRETARY OF DEFENSE
WASHINGTON 25, D. C.

MEMORANDUM FOR DR. MERVIN A. CASBERG, M. D.

SUBJECT: The standards and requirements to be followed in human experimentation.

It is recommended that the attached principles and conditions for human experimentation, which were laid down by the Tribunal in the Nuremberg Trials, be adopted instead of those previously submitted by me, with the following change:

In No. 5 delete everything after the word "occur" and insert the period after that word.

Add (1)(g) of previously submitted conditions to wit:

"11. Whereas prisoners incarcerated in penal institutions may and have been used if the required conditions are met, prisoners of war will not be used in human experimentation."

Stephen S. Jackson
Counsel

Attachments (3)

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5. No experiment should be conducted where there is an a priori reason to believe that death or disabling injury will occur.

6. The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.

7. Proper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability, or death.

8. The experiment should be conducted only by scientifically qualified persons. The highest degree of skill and care should be required through all stages of the experiment of those who conduct or engage in the experiment.

9. During the course of the experiment the human subject should be at liberty to bring the experiment to an end if he has reached the physical or mental state where continuation of the experiment seems to him to be impossible.

10. During the course of the experiment the scientist in charge must be prepared to terminate the experiment at any stage, if he has probable cause to believe, in the exercise of the good faith, superior skill and careful judgment required of him that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject.

11. Prisoners of war will not be used in human experimentation.

1 of 2 copies

OFFICE OF THE SECRETARY OF DEFENSE

1-4-53

MEMO FOR Mr Foster

I believe Mr Lovett has a considerable awareness of this proposed policy. It has been under development for some time.

Because of the importance and controversial character of the policy, I strongly recommend advance clearance with Service Sec'ys thru Joint Sec'y's group. If you agree, we'd like to recapture the case so that copies can be made available to Service Sec'ys.

Since consequences of this policy will fall upon Mr Wilson, it might be wise to pass to him as a unanimous recommendation from the "alumni".

gwl

C-30214

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ENTRY: #199

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OFFICE OF THE SECRETARY OF DEFENSE
ARMED FORCES MEDICAL POLICY COUNCIL
WASHINGTON 25, D. C.

JAN 12 1953

MEMORANDUM FOR THE SECRETARY OF DEFENSE

SUBJECT: Digest "Use of Human Volunteers in Experimental Research."

The Problem

Approval of the recommendation that human volunteers be used in experimental research in order to reach a realistic evaluation of protective methods against biological, chemical and/or atomic agents of warfare.

Factors Bearing on the Problem

1. Research which has been conducted in this field has been restricted in most part to experimental animals.

2. Results based entirely on animal experimentation cannot be interpreted as conclusive evidence of identical human reaction to similar situations. Such methods of extrapolation have in the past and will continue in the future to lead experimenters into serious errors.

3. In order for realistic evaluations to be made of the defensive measures which should be adopted to protect our Nation against a potential enemy attack with any one of the three types of agents, it is necessary to secure additional information which can be secured only through the use of human subjects.

4. The use of human volunteers shall be subject to the principles and conditions laid down as a result of the Nuremberg Trials, which will afford adequate protection to the individual participant, as well as the Government. One other restriction is added in that prisoners of war shall not be used under any circumstances.

Recommendation

It is strongly recommended that a policy be established for use of human volunteers (military and civilian employees) in experimental research at Armed Forces facilities.

Encl 1

Concurrences

This proposal has been concurred in by the following:

Assistant Secretary (Manpower & Personnel)
Assistant Secretary (Legal and Legislative Affairs)
Research and Development Board
Joint Staff (JCS)
Military Liaison Committee
Secretary of Joint Secretaries
Director of Administration, OSD

Melvin A. Casberg, M. D.
Chairman
Armed Forces Medical Policy Council

OFFICE OF THE SECRETARY OF DEFENSE
EXECUTIVE OFFICE OF THE SECRETARY
WASHINGTON 25, D. C.

5 February 1953

MEMORANDUM FOR MR. KYES

SUBJECT: Use of Human Volunteers in Experimental Research

This case involves the establishment of a Department of Defense policy prescribing conditions which will govern the use of human volunteers in experimental research in the field of atomic, biological and/or chemical warfare. There is no DOD policy on the books which permits this type of research.

This question has been under consideration for a long time. It was last considered at a meeting of the Joint Secretaries Group on 8 January 1953. Dr. Casberg, Chairman of the Armed Forces Medical Policy Council, briefed Mr. Foster and the three Service Secretaries (Mr. Lovett being before the Congress at the time) on the proposed policy. Although no specific objections were raised by the four Secretaries, neither was there any expression of enthusiasm in favor of the policy. The only agreement reached was that the decision should be deferred to Secretary Wilson in view of the controversial aspects of the policy and the fact that his administration would have responsibility for administering the policy if approved.

Mr. Foster informed me that he had discussed this question with you and suggested that I should submit the papers to you as soon as you opened for business.

Dr. Casberg is available to discuss the matter with you if you so desire.

Note:
This case has been revised to reflect discussion at meeting of AFPC on 17 Feb 53

G. V. UNDERWOOD, Jr.
Colonel, USA
Director, Executive Office

TOP SECRET
SECURITY INFORMATION

Washington

DoD

DNAI 940906.109

26 Feb 1953

MEMORANDUM FOR THE SECRETARY OF THE ARMY
SECRETARY OF THE NAVY
SECRETARY OF THE AIR FORCE

SUBJECT: Use of Human Volunteers in Experimental Research

1. Based upon a recommendation of the Armed Forces Medical Policy Council, that human subjects be employed, under recogniz safeguards, as the only feasible means for realistic evaluation and/or development of effective preventive measures of defense against atomic, biological or chemical agents, the policy set forth below will govern the use of human volunteers by the Department of Defense in experimental research in the fields of atomic, biological and/or chemical warfare.

2. By reason of the basic medical responsibility in connect with the development of defense of all types against atomic, biological and/or chemical warfare agents, Armed Services perso and/or civilians on duty at installations engaged in such resea shall be permitted to actively participate in all phases of the program, such participation shall be subject to the following conditions:

a. The voluntary consent of the human subject is absolutely essential.

(1) This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, over-reaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision. This latter element requires that before the acceptance of an affirmative decision by the experimental subject there should be made known to him the nature, duration, and purpose of the experiment; the method and means by

HRE-045

which it is to be conducted; all inconveniences and hazards reasonably to be expected; and the effects upon his health or person which may possibly come from his participation in the experiment.

(2) The concept of the human subject shall be in writing, his signature shall be affixed to a written instument setting forth substantially the aforementioned requirements and shall be signed in the presence of at least one witness who shall attest to such signature in writing.

(a) In experiments where personnel from more than one Service are involved the Secretary of the Service which is exercising primary responsibility for conducting the experiment is designated to prepare such an instrument and coordinate it for use by all the Services having human volunteers involved in the experiment.

(3) The duty and responsibility for ascertaining the quality of the consent rests upon each individual who initiates, directs or engages in the experiment. It is a personal duty and responsibility which may not be delegated to another with impunity.

b. The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature.

c. The number of volunteers used shall be kept at a minimum consistent with item b., above.

d. The experiment should be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problem under study that the anticipated results will justify the performance of the experimer

e. The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury.

f. No experiment should be conducted where there is an a priori reason to believe that death or disabling injury will occur.

g. The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.

h. Proper preparation should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability, or death.

i. The experiment should be conducted only by scientifically qualified persons. The highest degree of skill and care should be required through all stages of the experiment of those who conduct or engage in the experiment.

j. During the course of the experiment the human subject should be at liberty to bring the experiment to an end if he has reached the physical or mental state where continuation of the experiment seems to him to be impossible.

k. During the course of the experiment the scientist in charge must be prepared to terminate the experiment at any stage, if he has probable cause to believe, in the exercise of the good faith, superior skill and careful judgment required of him that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject.

1. The established policy, which prohibits the use of prisoners of war in human experimentation, is continued and they will not be used under any circumstances.

3. The Secretaries of the Army, Navy and Air Force are authorized to conduct experiments in connection with the development of defenses of all types against atomic, biological and/or chemical warfare agents involving the use of human subjects within the limits prescribed above.

4. In each instance in which an experiment is proposed pursuant to this memorandum, the nature and purpose of the proposed experiment and the name of the person who will be in charge of such experiment shall be submitted for approval to the Secretary of the military department in which the proposed experiment is to be conducted. No such experiment shall be undertaken until such Secretary has approved in writing the experiment proposed, the person who will be in charge of conducting it, as well as inform the Secretary of Defense.

5. The addressees will be responsible for insuring compliance with the provisions of this memorandum within their respective Services.

/signed/
C.E. WILSON

Copies furnished:
Joint Chiefs of Staff
Research and Development Board

[illegible] XII 2 March 1953

Doctor Colin M. MacLeod
College of Medicine
New York University
477 First Avenue
New York 16, New York

Dear Colin:

The attached copy of letter I believe is self-explanatory.

I learned today that the Secretary of Defense signed the document we saw, but that there was some modification in the phrase "even remote possibility". In any case Dr. Casberg pointed out, it only applies to the limited spheres enumerated in the beginning. He also gave instructions that everything be done to insure that the hepatitis experiments proceed, and if necessary, that a specific policy statement be prepared and issued. Mr. Jackson agreed, but stated that the policy statement should be so drawn up that:

a. the responsibility that the experiments were necessary, feasible, and that the scientific, ethical, and legal considerations were reviewed and approved, was firmly delegated to either the Armed Forces Medical Policy Council or the Armed Forces Epidemiological Board, preferably the latter; and

b. that the Secretary of Defense was not left "holding the bag".

It was on Mr. Jackson's insistance that the "Nuremberg Principles" were used in toto in the document, since he stated, these already had international juridical sanction, and to modify them would open us to severe criticism along the line - "see they use only that which suits them".

Sincerely yours,

ADAM J. HAPALSKI
Colonel, M. C.
Administrator,
Armed Forces Epidemiological Board

Incl.
Cpy ltr to
Dr. Karsner

cpy except for Alumni Bull
Nuremberg Code

R

COPIED: 12/1/94
RECORD GROUP: #334
ENTRY: #14
FILE: Commission on Liver Diseases - Administration
Committee on Allocation of Volunteers

COPY

[redacted]

COPY

- CS Memo.

DEPARTMENT OF THE ARMY
Office of the Chief of Staff
Washington 25, D. C.

CS: 385 (30 Jun 53)

30 June 1953

MEMORANDUM THRU: ASSISTANT CHIEF OF STAFF, G-4

FOR: CHIEF CHEMICAL OFFICER
THE SURGEON GENERAL

Regraded [redacted]
By authority of [redacted]
Dept of Army
by ELDON V. [redacted]
Classification Chief [redacted]

SUBJECT: Use of Volunteers in Research for defense against ABC warfare

1. This directive prescribes policies and procedures governing the use of volunteers in research in defense against atomic, biological and chemical warfare. The purpose of this research is to permit a realistic evaluation and/or development of effective preventive measures of defense against atomic, biological or chemical agents.

2. Certain basic principles must be observed in order to satisfy moral, ethical and legal concepts. These basic principles are:

a. The voluntary consent of the human subject is absolutely essential.

(1) This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, over-reaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision. This latter element requires that before the acceptance of an affirmative decision by the experimental subject there should be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonably to be expected; and the effects upon his health or person which may possibly come from his participation in the experiment.

(2) The consent of the human subject shall be in writing, his signature shall be affixed to a written instrument setting forth substantially the aforementioned requirements and shall be signed in the presence of at least one witness who shall attest to such signature in writing.

(a) In experiments where personnel from more than one Service are involved, the Secretary of the Service which is exercising primary responsibility for conducting the experiment is designated to prepare such an instrument and coordinate it for use by all the Services having human volunteers involved in the experiment.

Incl 1

[redacted]

SUBJECT: Use of Volunteers in Research

(3) The duty and responsibility for ascertaining the quality of the consent rests upon each individual who initiates, directs or engages in the experiment. It is a personal duty and responsibility which may not be delegated to another with impunity.

b. The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature.

c. The number of volunteers used shall be kept at a minimum consistent with item b. above.

d. The experiment should be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problem under study that the anticipated results will justify the performance of the experiment.

e. The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury.

f. No experiment should be conducted where there is a prior reason to believe that death or disabling injury will occur.

g. The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.

h. Proper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability, or death.

i. The experiment should be conducted only by scientifically qualified persons. The highest degree of skill and care should be required through all stages of the experiment of those who conduct or engage in the experiment.

j. During the course of the experiment the human subject should be at liberty to bring the experiment to an end if he has reached the physical or mental state where continuation of the experiment seems to him to be impossible.

k. During the course of the experiment the scientist in charge must be prepared to terminate the experiment at any stage, if he has probable cause to believe, in the exercise of the good faith, superior skill and careful judgment required of him that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject.

SUBJECT: Use of Volunteers in Research

(1) The established policy, which prohibits the use of prisoners of war in human experimentation, is continued and they will not be used under any circumstances.

3. The following opinions of the Judge Advocate General furnish specific guidance for all participants in research in atomic, biological and/or chemical warfare defense using volunteers.

a. Legality of accepting volunteers. The authority of the Secretary of the Army to conduct research and development activities is contained in section 104 of the act of 10 July 1950 (64 Stat. 322; 5 U.S.C 235a) which provides:

> "The Secretary of the Army is authorized to conduct, engage, and participate in research and development programs related to activities of the Army of the United States and to procure, or contract for the use of, such facilities, equipment, services, and supplies as may be required to effectuate such programs."

Section 101 of the Army Organization Act of 1950 (64 Stat. 264; 5 U.S.C. 181-4) provides in part as follows:

> "Except as otherwise prescribed by law, the Secretary of the Army may make such assignments and details of members of the Army and civilian personnel as he thinks proper, and may prescribe the duties of the members and civilian personnel so assigned; and such members and civilian personnel shall be responsible for, and shall have the authority necessary to perform, such duties as may be so prescribed for them."

b. Military Personnel and Department of the Army Civilian Employees. Compensation for the disability or death of a civilian employee resulting from personal injury or disease proximately caused by his employment is payable under the Federal Employees Compensation Act (39 Stat. 742 et seq.), as amended (5 U.S.C. 751 et seq.), regardless of whether his employment was of a hazardous nature. The amount and type of disability compensation or other benefits payable by reason of the death or disability of a member of the Army resulting from injury or disease incident to service depends upon the individual status of each member, and is covered by various provisions of law. It may be stated generally that under present laws no additional rights against the Government will result from the death or disability of military and civilian personnel participating in experiments by reason of the hazardous nature of the operations although it is possible that the Congress may confer benefits or grant relief by general or special legislation subsequently enacted. Even should the injury or disease result from a negligent or wrongful act, the recovery of any compensation or benefit under present law in addition to those noted above is doubtful

SUBJECT: Use of Volunteers in Research

c. Use of Appropriated Funds for the Purchase of Life Insurance. In effect, the payment of insurance premiums on the life of an officer or employee is a form of compensation (Commissioner of Internal Revenue vs. Benwit, 87 F. 2d 764 (2nd Dir., 1937), cert. den. 302 U.S. 694, 82 L. Ed. 536: Canaday v. Guitteau, 86 F. 2d 303 (6th Cir., 1936). In this regard, section 1765 of the Revised Statutes (5 U.S.C. 70) provides as follows:

> "No officer in any branch of the public service, or any other persons whose salary, pay, or emoluments are fixed by law or regulations, shall receive any additional pay, extra allowance, or compensation, in any form whatever, for the disbursement of public money, or for any other service or duty whatever, unless the same is authorized by law, and the appropriation therefor explicitly states that it is for such additional pay, extra allowance, or compensation."

There is no statutory authority for the payment of premiums for insuring the lives of military and civilian personnel, and current appropriations for military and civilian pay and allowances do not expressly provide therefor. It follows that the payment of such premiums from appropriated funds is prohibited by the quoted section. The statutory provision in question is applicable to all military and civilian personnel of the Army "whose salary, pay, or emoluments are fixed by law or regulations" (24 Comp. Gen. 648 (1945).

d. Private Citizens. Section 3679 of the Revised Statutes, as amended (31 U.S.C. 665(b)), provides:

> "No officer or employee of the United States shall accept voluntary service for the United States or employ personal service in excess of that authorized by law, except in cases of emergency involving the safety of human life or the protection of property."

It is the policy of the quoted statute to prohibit the acceptance of voluntary services which may provide a basis for future claims against the Government. The stated policy applies not only where legal claims for compensation may arise from performance of the services, but also where the circumstances surrounding the proffer support a reasonable possibility that the services may provide the basis for seeking remedial legislation from the Congress. The JAG is therefore of the opinion that the services in question should not be accepted by the Department of the Army. In view of this conclusion, it is unnecessary to consider the extent to which such persons could exert claims against the Government by reason of disability or death resulting from participation in the proposed experiments, or whether premiums on life insurance for the said participants may be paid from appropriated funds.

c. Contractors' employees. The applicability of the foregoing considerations to contractors' employees is considered below:

(1) Legality of employment. The authority of the Secretary of the Army to contract for services necessary to effectuate research and development activities is contained in section 104 of the act of 10 July 1950 (64 Stat. 322; 5 U.S.C. 235a), quoted in subparagraph a, above. There appears to be no provision of law which would prevent a contractor from employing his personnel upon experiments of the nature contemplated. In the literal sense, no question of "acceptance" of the services in question by the Government is involved, as the private relation of such an employee is with the contractor rather than the Government. It devolves upon the contracting officer to ascertain whether the terms are sufficiently broad to permit the participation of contractor employees in the experiment. The terms of the contract must insure that the contractor will observe the conditions and safeguards set forth in this directive.

(2) Claims against the Government. Generally, benefits to which a private employee may become entitled by reason of death or disability resulting from his employment are payable under State, rather than Federal, laws, with the exception of persons covered by the survivor's insurance provisions of the Social Security Act (49 Stat. 623), as amended (42 U.S.C. 402). In some situations the employee may have remedies against his employer under State workmen's compensation or other laws. It is not possible to generalize upon the right of such an employer, where he is a Government contractor, to claim reimbursement from the Government for additional costs by reason of liability to his employees incurred in this regard, as this depends upon the terms of each individual contract. The question of whether any additional rights against the employer-contractor may result from the death or disability of employees participating in experiments, by reason of the hazardous nature of the experiments, is likewise not susceptible of any general statement, due to the numerous factors involved. Such persons would not be disqualified from prosecuting claims aginst the Government under the Federal Tort Claims Act (26 U.S.C. 2671 et seq.). (See also AR 25-70, 2 March 1951)

(3) Purchase of life insurance. In cost-reimbursable type contracts, the expense of maintaining group accident and life insurance plans may be an allowable item of cost under the contract (ASPR 15-204(p). Group life insurance plans provided voluntarily to contractors' employees on a reimbursable basis are subject to review by heads of procuring activities to determine that greater benefits are not being extended under the cost-reimbursement type contract than those granted to employees under the contractor's regular commercial operations (APP 10-351). In special cases, life insurance for employees may be authorized by heads of procuring activities (ASPR 10-302; APP 302) even in fixed-price contracts (APP 10-301). In order to be applicable, cost principles

must be set forth or incorporated in a cost-reimbursable contract (ASPR 15-102). It will be seen from the above that, if a contractor obtains insurance on the lives of his employees while participating in the proposed experiments, he may be reimbursed for the expenses involved only where the contract is of a type allowing reimbursement and the terms thereof allow recovery as an item of cost.

f. Irregular and Fee-basis Employees. The stated category comprehends all persons paid from appropriated funds for intermittent services, as distinguished from regular, full-time employees. For example, the Secretary of the Army may procure the temporary or intermittent services of experts or consultants, including stenographic reporting services, without regard to civil service and classification laws at rates not to exceed $50 per diem (sec. 15, act of 2 Aug 1946 (60 Stat. 810;5 U.S.C. 55a); sec. 601, Department of Defense Appropriation Act, 1953 (Pub. Law 488, 82nd Cong.); see CPR A7.6, par. 6-3). The employment of experts and consultants either on a per diem basis or without compensation is also authorized by section 710, Defense Production Act of 1950 (64 Stat. 819; 50 U.S.C. App. 2160). (See CPR A7.6, par. 6-3). The Secretary of the Army may also employ architects, engineers, and other technical and professional personnel on a fee basis, without regard to classification laws (sec. 2, act of 7 Aug. 1939 (53 Stat. 1240; 5 U.S.C. 221)).

In general, the employment status of such persons must be determined individually from the statutory authority under which they are employed and the terms and conditions of their employment agreements. In some cases it will be found that their status is not that of employees, but of contractors furnishing services to the Government at agreed contract prices. The following observations are made upon the applicability of the three questions considered in subparagraph c, above, to the category of persons under consideration:

(1) Legality of accepting volunteers. The terms of the statutory authority for the employment and the provisions of the employment agreement must be inspected in each case to determine whether the particular individual is an employee subject to detail or assignment upon the proposed experiments, or whether his employment is limited to other specific objects. If his employment upon the project is not so authorized, it would appear that acceptance of his services for this purpose on a voluntary basis would be prohibited by the considerations discussed in subparagraph d, above.

(2) Claims against the Government. The Federal Employees Compensation Act (39 Stat. 742 et seq.), as amended (5 U.S.C. 751 et seq.), is applicable to "all civil officers and employees" of the Government and all "persons rendering personal services of a kind similar to those of civilian officers or employees of the United States* * *without compensation or for nominal compensation, in any case in which acceptance or use of such services is authorized by an Act of Congress or in which provision is made

by law for payment of the travel or other expenses of such person." The foregoing broad coverage of the act would appear to include most irregular and fee-basis employees. However, the administration of the benefits in question are within the province of the Bureau of Employees Compensation, Department of Labor, and only that agency may provide a definitive ruling with respect to coverage of the individuals in question. With the foregoing reservation, the views of this office set forth in subparagraph b, above, would appear equally applicable to irregular and fee-basis employees.

(3) Purchase of life insurance. The Comptroller General has approved the payment of surgical and hospitalization expenses of a field employee injured while engaged upon flood control work (3 Comp. Gen. 57 (1923)), on the ground that "the employee's compensation was not fixed by law but was subject to administrative discretion, since, otherwise, payment of the expense by the Government would constitute payment of additional compensation, which is prohibited by section 1765, Revised Statutes" (23 Comp. Gen. 175 (1946). Subject to such restrictions and limitations as may appear in the statutory authority under which he is employed, it would appear from the foregoing that the Government may legally bear the expense of premiums upon the life of an irregular or fee-basis employee whose rate of compensation is not fixed by law or regulations. In this regard, it may be advisable for the Government to provide an additional allowance to the employee for financing such private insurance arrangements as he may wish to make rather than to undertake direct negotiations with insurance carriers for the desired coverages.

4. Subject to the above conditions, Armed Forces personnel and/or civilians on duty at installations engaged in research in subject fields shall be permitted to actively participate in all phases of the program. As a general rule, volunteer subjects should be males under 35 years of age, with no physical or mental diseases.

5. Agents used in research must have the following limiting characteristics:

a. Controllable lethality.

b. No serious chronicity anticipated.

c. Effective therapy available.

d. Adequate background of animal experimentation.

6. As added protection for volunteers, the following safeguards will be provided:

SUBJECT: Use of Volunteers in Research

a. Direct responsibility for the planning and conduct of the investigations and for the medical care will rest with one adequately trained physician.

b. All apparatus and instruments necessary to deal with any emergency situations must be available, e.g., Drinker respirator, Mine Safety Pneophore, oxygen apparatus, etc.

c. Medical treatment and hospitalization will be provided for all casualties of the experimentation as required.

d. The physician in charge will have available to him on short notice throughout the investigation competent consultants representing any of the specialties to be encountered.

7. Due to the specialized nature of biological agents, the following procedures in addition to the foregoing policies and procedures will be observed in regard to this phase of the program.

a. In selecting agents for investigation, priority should be given to those which possess a high probability of successful infection under operational conditions against U. S. forces.

b. The effectiveness of available defensive measures, either immunization or chemoprophylaxis, will determine the necessity for study of the agent considered.

c. Use enlarged (4X) Henderson or other suitable apparatus for exposure.

d. First experiments will be designed to determine level of susceptibility. The investigation should utilize the minimum number of volunteers which will yield statistically valid data at low levels of dosage.

e. Increase number of persons to that level which will give significance.

f. Then use immunized persons and persons on prophylactic chemotherapy.

g. Determine and apply details of immunologic study.

h. From the foregoing the final step will be to use volunteer subjects, or if there exists a good correlation with a particular animal for a particular micro-organism, then use that animal, on a proving ground, downwind far enough from the munition so that the concentration will be known to be approximately equal to the level required to induce infection. (This will rule out subjecting volunteers to "crash" concentrations.)

CANCELLED

SUBJECT: Use of Volunteers in Research

8. No research in atomic, biological and/or chemical agents using volunteers will be undertaken until the Secretary of the Army has stated his approval in writing. The Surgeon General of the Army will review and comment on all proposals for the use of volunteers. When appropriate, he will seek the advice of The Surgeon General of the Navy, Air Force and/or the U. S. Public Health Service. The sponsoring Army agency will submit its proposal, together with the Surgeon General's review and comment thereon, to the Secretary of the Army through this office. As a minimum, the proposal will state the nature and purpose of the experiment and the name of the person who will be in charge.

BY DIRECTION OF THE CHIEF OF STAFF:

/s/ JOHN C. OAKES
Brigadier General, GS
Secretary of the General Staff

Copies furnished:
Asst. Chief of Staff, G-4 - 5
Chief Chemical Officer -5
The Surgeon General - 5
The Judge Advocate General - 5
Chief of Research and Development, OCS - 5

HHS 090794-F1

November 17, 1953

GROUP CONSIDERATION OF CLINICAL RESEARCH PROCEDURES DEVIATING FROM ACCEPTED MEDICAL PRACTICE OR INVOLVING UNUSUAL HAZARD*

It is the policy of the National Institutes of Health to place primary responsibility for the formulation and conduct of clinical research and medical care on the principal investigators designated by each Institute Director, in conformity with standards and principles of legal, ethical and administrative propriety established by the Director of the National Institutes of Health.

In order to assist the principal investigator in making determinations with respect to research projects and medical procedures which may involve deviation from accepted medical practice or potential hazard to the life or well-being of the patient or subject admitted to the Clinical Center, the following statement of responsibility is provided as guidance, and methods for obtaining group consideration and advice are established.

It will not be necessary to present each project for evaluation of its medical, scientific and ethical propriety to any single central group, but any unestablished, nonstandard or unusually hazardous procedure shall receive appropriate group consideration before it is undertaken.

I. Basic Responsibility

1. Patient Care Responsibility

Only properly qualified physicians or dentists may assume responsibility for clinical diagnosis, investigation and care. All others associated with the project are subject to the authority of the responsible physician or dentist, and the physician or dentist assumes responsibility for such personnel.

2. Project Formulation

It is recognized that every medical procedure is modified or adapted to accommodate the individual patient. It also contains some element of risk. Determination as to which medical procedures shall be considered as not being established or as involving unusual hazard shall be on an individual basis, in the light of total experience developed in well recognized institutions accepted by the profession for the excellence of their staff in conducting medical care and research. Published reports

*Approved by Director, NIH

of techniques or procedures used elsewhere in clinical investigation without known deleterious effect to the subject will not, of themselves, relieve the investigator from responsibility for submitting for group consideration his plans to use the same or similar methods.

Two distinct types of hazard are recognized: (a) Jeopardy to the life or relative state of well-being of the research subject, either a person suffering from disease whether considered curable or incurable, or a normal volunteer subject; (b) Jeopardy to the subject's chances for cure of his illness or alleviation of his symptoms, occasioned by withholding or delaying the application of established therapeutic procedures.

In the development of any clinical study involving procedures deviating from accepted medical practice or involving unusual hazard, the principal investigator shall indicate, as prescribed by the Director of his Institute, such contemplated procedures, referring to the literature and his own and others' experience. He shall indicate the necessity and basis for his proposed research, noting pertinent laboratory, animal and other human research and, insofar as possible, the potential hazard to the patient or subject.

3. Public Health Service Personnel

Self-experimentation and use of Public Health Service personnel as subjects in clinical investigation are prohibited, unless prior written consent is granted by the Director of the National Institutes of Health.

II. Group Consideration and Review

1. Institute Committees

Each Institute Director and the Director of the Clinical Center shall establish a committee or other mechanism to review and make recommendations to him concerning clinical projects proposed by his staff that involve unusual hazard. The review shall include evaluation of the necessity and rationale of any such procedure, all significant questions concerning medical or ethical propriety of the procedure, availability of personnel or facilities to reduce hazard, and other issues requiring experienced group judgment. The committee shall recommend (1) approval with or without modification, (2) disapproval, or (3) referral to the Medical Board.

In general this review is expected to settle such matters without further referral. The principal or senior investigator, who is responsible for project formulation and eventual conduct of the research, may through channels request his Institute Director to seek further advice or guidance from the Medical Board.

2. Medical Board Committee

The Medical Board shall establish a Clinical Research Committee to

serve as an expert review body to advise on problems concerning clinical research involving procedures deviating from accepted medical practice or unusual hazard referred to it by the Director of the National Institutes of Health, institute or clinical directors, or the Director of the Clinical Center. The Committee is authorized to enlist additional assistance on an ad hoc basis from among colleagues, intramural and extramural, consultants and others who may have greater experience and competence in relation to a given problem.

This committee will investigate the scientific and ethical propriety, and provide group consideration, before the institution of any procedure about which such questions have been raised. Recommendations of this Committee will be submitted through the Medical Board to the institute concerned and to the Director, National Institutes of Health, for his information or advice.

3. Public Health Service Policy Committee

A small standing policy committee for the Public Health Service, composed of representatives of the National Institutes of Health and other bureaus, will develop a set of guides and principles relative to human research and serve as a general review body and staff for the Surgeon General. Special problems of major significance which should receive Service-wide consideration or which impinge on general policy may be submitted to this group, by the Director of the National Institutes of Health, institute or clinical directors, or the Director of the Clinical Center.

III. Principles Governing Physician-Patient Relationship

1. Rules of Conduct

Rules of conduct promulgated by the appropriate national professional organization to govern the relationship between the professional man and his patient shall be observed by staff of the National Institutes of Health.

2. Information for Patient

The patient or subject of clinical study shall be considered a member of the research team and shall be afforded an understanding suited to his comprehension of the investigation contemplated, including particularly any potential danger to him.

Each prospective patient will be given an oral explanation in terms suited to his comprehension, supplemented by general written information or other appropriate means, of his role as a patient in the Clinical Center, the nature of the proposed investigation and particularly any potential danger to him.

After admission, the patient shall receive information in keeping with the development of a sound physician-patient relationship.

3. Patient Understanding and Agreement

a. Standard consent or agreement forms shall be used for surgery, anesthesia, photography and other procedures where they are ordinarily required and for permission to disclose clinical findings, records or other personal infomation.

b. Similarly, standard forms pertaining to post-mortem examination and disposal of body or limbs shall be used to record permission for such procedures given by responsible next of kin or legal representative.

c. Voluntary agreement based on informed understanding shall be obtained from the patient and, when appropriate, from responsible next of kin when the approved investigation includes procedures which deviate from accepted medical practice. In all such cases, a notation shall be made on the patient's chart of the essential points of the explanation and of the agreement obtained, together with any comment or problems raised by the patient. When in the opinion of the responsible physicians or of the advisory groups noted above a procedure involves an unusual hazard, the proposed procedure shall not be undertaken until the patient has voluntarily signed a statement, entered on the patient's chart or as a separate memorandum, indicating his understanding of the procedure and its purpose, including potential hazards to him, and his willingness to participate.

4. Responsibility

The physician in charge of the patient shall be finally responsible for providing information to the patient, referring physician and next of kin and for obtaining voluntary agreement from the patient, guardian, next of kin or others, as required, for the procedures described above. He shall be responsible for incorporating in the medical record the information given the patient and the nature of the informed consent or agreement accomplished with the patient, including any comments, objections or general reactions made by the patient.

[redacted] This document consists of 2
No. 3 of 7 Copies, Series

SWPSG/700

SUBJECT: Status of Human Volunteers in Bio-medical Experimentation

TO: Assistant Secretary of Defense (Health & Medicine)
Office, Secretary of Defense
Washington 25, D. C.
ATTN: Colonel Sheldon S. Brownton

1. In carrying out its responsibilities with regard to the public release of atomic energy information under the provisions of Department of Defense Directives Nos. S-5400.2, dated 22 September 1952, and 5230.4, dated 26 November 1952, the Office of Public Information requires Headquarters, Armed Forces Special Weapons Project to review and comment on releases involving the military application of atomic energy. The scope of review of documents taken by this headquarters is limited to the following:

a. Comment is made from the security classification standpoint of the military application of atomic energy.

b. Comment is made on technical inaccuracies from the standpoint of the military application of atomic energy.

2. In implementing this policy, the Surgeon, Headquarters, AFSWP, is frequently required to review documents containing Bio-medical experimental data obtained either by laboratory studies or from atomic weapons tests. Some of these documents contain data obtained by, and make reference to, the use of human volunteers as test subjects.

3. The Surgeon also reviews all proposals for Bio-medical research projects programmed at atomic weapons tests by other agencies as well as initiating and sponsoring such proposals. Some of these projects include the use of human volunteers.

[redacted]

OFFICE SYMBOL	1.	2.	3.	4.	5.
GRADE AND SURNAME OF COORDINATING OFFICERS					

HRE-0421

SWPSG/700
Subject: Status of Human Volunteers in Bio-medical Experimentation

4. At the present time, this headquarters is reviewing a technical report entitled "Flash Blindness" which mentions the fact that human volunteers were employed during atomic weapons tests conducted in 1951. Subsequent reports from later tests on the same subject contain comparable references as well as referring to at least two instances in which volunteers were injured as a consequence of taking part in field experiments. Because of the implications involved due to these injuries, it is felt that a definite need exists for guidance in the use of human volunteers as experimental subjects.

5. It is therefore requested that this headquarters be advised if such guidance is available and, if so, that a copy of the policy directive be made available for reference. If such policy guidance has not been formulated, it is recommended that such be done and given the widest possible dissemination to preclude the occurrence of unintentional violations or incidents by research investigators.

DISTR:
Cys 1 & 2 (letterhead) to addressee
Cy 3 (green) to AG
Cy 4 (yellow) to AG
Cy 5 (pink) to AG
Cy 6 (white) Medical Branch reading file
Cy 7 (white) Medical Branch comeback file copy

FOR THE CHIEF, AFSWP:

IRVING L. BRANCH
Colonel, USAF
Actg. Chief of Staff

(SEE NEXT PAGE FOR M/R)

Lt. Col. Browning/mef/1B699A/52793
SECOND PAGE REWRITTEN Major Miller/ned/1B699A/52793 3-5-54

[redacted]

OFFICE SYMBOL	1. SWPEP	2. SWPSV	3. SWPSC	4. SWPCS	5. SWPAG
GRADE AND SURNAME OF COORDINATING OFFICERS					

D-64256

M/R: In Nov 53 it was learned that there existed a T/S document signed by the Secretary of Defense which listed various requirements and criteria which had to be met by individuals contemplating the use of human volunteers in Bio-medical or other types of experimentation. Since this information was of particular importance to this office in classifying and/or releasing information on the Flash Blindness programs at weapons tests, attempts were made to learn of the nature of these requirements. On 14 January 1954, Lt. Colonel Browning and Major Miller had a conference with the Executive Assistant to the Assistant Secretary of Defense (Health and Medical) at which time it was learned that although this document details very definite and specific steps which must be taken before volunteers may be used in experimentation, no serious attempt has been made to disseminate the information to those experimenters who had a definite need-to-know. The lowest level at which it had been circulated was that of the three Secretaries of the Services. The Assistant Secretary and his Executive agree that the document should be downgraded but have not been able to obtain concurrence from Dr. Hannah nor from the Judge Advocate. It was suggested that this office prepare a letter for the Assistant Secretary in which was detailed our need for this information and the manner in which we were handicapped through ignorance of the provisions of this document. It is intended that this letter shall point up the need for some relaxation of the grip in which this document is now held, at least on a definite need-to-know basis.

700

Lt. Colonel Browning/mef/1B699A/52793
SECOND PAGE REWRITTEN Major Miller/ned/1B699A/52793 3-5-54

OFFICE SYMBOL	1. SWPSC	2. SWPEF	3. SWPSV	4. SWPCS	5. SWPAG
GRADE AND SURNAME OF COORDINATING OFFICERS	H Jaeger	Maj Keeller	Maj Smith		
	[redacted]				

D-64256

AFSWP ROUTING AND CONTROL SHEET

SECRET

NOTE: This Routing and Control Sheet will remain attached to this communication until all action required is completed. After action has been completed it will be filed in the Adjutant General's Office.

TO:		INITIALS	DATE	FOR
SA	CHIEF, AFSWP			APPROVAL
	DEPUTY CHIEF, USAF			COMMENT
	DEPUTY CHIEF, USN			CONCURRENCE
25	CHIEF STAFF	[illegible]	2/25	INFORMATION
	OCS/OPERATIONS			NECESSARY ACTION
	CHIEF, PLANS AND RQMTS			NOTE AND FORWARD
	CHIEF, OPNS AND TNG			NOTE AND RETURN
X	OCS/ADMINISTRATION [illegible]	[illegible]	2/25	COORDINATION
3	CHIEF, SECURITY SC-3	[illegible]	25 Feb	FILE IN AGO
	CHIEF, PERSONNEL			SIGNATURE
	CHIEF, LOGISTICS			
2	OCS/TECHNICAL SERVICES	[illegible]		
	CHIEF, WPNS DEV			
1	CHIEF, WPNS EFFECTS	[illegible]	25 Feb	
	CHIEF, WPNS DEFENSE			
	CHIEF, WPNS TEST		1 1	
26	ADJUTANT GENERAL	[illegible]	7/27	
	INSPECTOR GENERAL			
	SPECIAL ASST TO CHIEF, AFSWP			
	HISTORIAN			
	SURGEON			

DATE RECEIVED

CONTROL NUMBER

EF-126

FILE NUMBER

SWPSG/700

SUSPENSE DATE

TYPE OF COMMUNICATION; NUMBER OF COPIES, INDORSEMENTS AND INCLOSURES

Letter to Assistant Secretary of Defense

FROM:

Surgeon's Office

DATE

10 Feb 1954

SUBJECT OR SUMMARY OF THE COMMUNICATION

Status of Human Volunteers in Bio-Medical Experimentation

REMARKS

Cys 1 & 2 (white letterhead) to addressee
Cy 3 (green) to AG
Cy 4 (yellow) to AG
Cy 5 (pink) to AG
Cy 6 (white) Surgeon's Reading File
Cy 7 (white) Surgeon's comeback copy for file

(Oiston Green)
(File No.)

Declassified by DNA, Chief, ISTS

DATE: 8/23/90

SECRET

AFSWP FORM 4
1 OCT 52

EDITION OF 1 SEP 52. MAY BE USED.

GPO 16—67612-1

S-22

(NOT FOR PUBLICATION) 12 March 1954

Use of Human Volunteers in Medical Research
Principles, Policies and Rules of the Office of The Surgeon General
(To be used as far as applicable as a non-mandatory guide for planning and conducting contract research.)

1. The voluntary consent of the human subject is essential. This means that the person concerned:

a. Should have legal capacity to give consent.

b. Should be so situated as to be able to exercise free power of choice, without intervention of force, fraud, deceit, duress, over-reaching, or other form of constraint or coercion.

c. Should have sufficient knowledge and understanding of the experiment to enable him to make an enlightened decision, on the basis of explanation given to him as specified below.

d. Should state his consent in writing, signed in the presence of at least one witness who shall attest to such signature in writing.

2. Each individual who initiates, directs or engages in the experiment has a personal duty and responsibility for ascertaining the quality of the volunteer's consent.

3. Before the acceptance of consent of the volunteer, he must be given adequate explanation. He should be informed of the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonably to be expected; and the effects upon his health or person which may possibly come from his participation in the experiment.

4. The experiment should be such as to yield fruitful results for the good of society, unprocurable by other means of study, and not random and unnecessary in nature.

5. The number of volunteers used must be kept at a minimum consistent with the requirement of a fruitful experiment for the good of society.

6. In order that the anticipated results will justify doing the experiment, it (the experiment) should be designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problem under study.

7. The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury.

8. No experiment should be conducted where there is a priori reason to believe that death or disabling injury will occur.

9. The degree of risk to the volunteer should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.

10. The experiment should be conducted only by scientifically qualified persons (including an adequately trained physician) who shall be required to exercise the highest degree of skill and care throughout the experiment. Competent consultants should be available on short notice in this connection.

11. Adequate preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability or death. This includes hospitalization and medical treatment as may be required.

12. The human volunteer subject should be at liberty to bring the experiment to an end if he feels that it is impossible for him to continue under the test.

13. The scientist or physician in charge must be prepared to terminate the experiment at any stage, if he has probable cause to believe, in the exercise of the good faith, superior skill and careful judgment required of him that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject.

14. Established policy prohibits the use of prisoners of war in human experimentation. They will not be used under any circumstances.

15. Agents used in research must have the following limiting characteristics:

a. Controllable lethality

b. No serious chronicity anticipated

c. Effective therapy available

d. Adequate background of animal experimentation.

LETTERMAN ARMY HOSPITAL
SAN FRANCISCO, CALIFORNIA

ADDRESS REPLY TO
COMMANDING GENERAL
NOT TO INDIVIDUALS

14 January 1955

Colonel Elmer A. Lodmell, M.C.
Chief, Radiological Service
Walter Reed Army Hospital
San Francisco, California

Dear Elmer:

I am writing you this letter at the suggestion of General Gillespie after having discussed with him the matter of requiring patients to sign a permit for radioisotope therapy. We have started in a small way, limiting outselves to test doses of I^{131}. Work has been started on the Radioisotope Laboratory and should be completed within 90 days.

In our initial meeting of the Radioisotope Committee it was tentatively decided that we would not require a signed permission on the part of the patient for test doses. This conforms with the practice at Stanford Hospital but does not conform with the practice at University of California Hospital where Dr. Miller requires a signed permission even for test doses. However, he tells me that he is not sure that this is advisable and that it is mainly a continuation of a practice initiated when the procedure was still experimental and also because on the form the patient is required to sign a statement that she is not pregnant. Regarding the signed permission for therapeutic doses we could not reach complete agreement since Major Langdon, who is in charge of the Radioisotope Laboratory feels that it is not indicated and, if utilized in the form now used at Walter Reed in which possible malignant change is mentioned, that it will have an adverse effect on the patient with hyperthyroidism. Major Newman feels that one should be signed but is not convinced that the reference to malignancy is desirable. The Legal Officer (Lt. John J. Mullane, Jr, Asst. Judge Advocate) states that, if the permission is to stand up in court, all possible deleterious effects including malignant change must be explained to the patient and signature obtained. I feel that a signed permission should be obtained but doubt the wisdom of mentioning the possible malignant change since there is no definite evidence that this has ever occurred. The Radioisotope Committee could not agree on what should be done and General Gillespie suggested this letter to find out if an Army-wide policy has been or would be established.

I have talked to Dr. Miller and I am enclosing a copy of the form which they require signature on which impresses me as a quite innocuous form although the wording I believe could be improved upon. I am told that a signed form is required at Stanford by Dr. Newell but he is out of town and I can get no information.

I would also like to know if you approve of the authorization used at Walter Reed Hospital for radiophosphorus and also radio iodine in the treatment of thyroid cancer, copies of which I am enclosing.

Any information you can give me along these lines will be greatly appreciated.

Sincerely,

Paul.

PAUL O. WELLS
Colonel, M.C.
Chief, Radiological Service

 Walter Reed A.M.

List of Specific Uses of Radiomaterials with Suggested Additions (As additional Paragraphs) to the "AUTHORIZATION FOR ADMINISTRATION OF RADIOACTIVE MATERIALS"

Form For the Purpose of Further Clarification

1. Radioiodine (I^{131}) for treatment of hyperthyroidism:

The expected beneficial results and the possible undesirable results (the latter including such real possibilities as sore throad and hypothyroidism and such speculative possiblities as malignant changes) of this form of treatment have been explained to me to my satisfaction.

2. Radiophosphorus (P^{32}) for treatment of leukemia or polycythemia vera:

The expected beneficial results and the possible undesirable results (the latter including radiation sickness and depression of the blood-forming functions of the bone marrow) of this form of treatment have been explained to me to my satisfaction.

3. Radioiodine (I^{131}) for inducing hypothyroidism in euthyroid patients with incapacitating angina pectoris and/or chronic congestive heart failure:

The expected beneficial results and the possible undesirable results (the latter including such a real possibility as sore throat and such speculative possibilities as sterility and malignant changes) of this form of treatment have been explained to me to my satisfaction. Also I understand that this treatment is for the purpose of destroying all thyroid tissue, normal as well as diseased; and, that a permanent need for replacement therapy in the form of thyroid medication must be expected if a normal metabolic state is to be maintained.

CLINICAL RECORD | AUTHORIZATION FOR ADMINISTRATION OF RADIOACTIVE MATERIALS

1. I hereby consent to the performance upon: _____

of _____
(Diagnostic and/or therapeutic Procedure to be performed)

_____
(Signature of Patient)

When patient is unable to affix signature or is legally incompetent:

WITNESSED BY: _____
(Signature of Consenting Person)

_____
(Relationship to Patient)

_____
(Signature of Witness)

_____
(Address)

_____ _____
(Date) (City & State)

Patient's Name (Last, First & Middle Name) | Register No. | Ward No.

Name of Hospital or Other Medical Facility

WRAMC Form 803
15 Dec 1954

4. Radioiodine (I^{131}) for treatment of thyroid cancer:

The expected beneficial results and the possible undesirable results (the latter including such a real possibility as sore throat and such speculative possibilities as sterility and malignant changes) of this form of treatment have been explained to me to my satisfaction. Also, I understand that this treatment is for the purpose of destroying all thyroid tissue, normal as well as diseased; and, that a permanent need for replacement therapy in the form of thyroid medication must be expected if a normal metabolic state is to be maintained.

5. Radiogold (Au^{198}) for intracavitary instillation in the treatment of effusions due to malignancies:

The expected beneficial results and the possible undesirable results (the latter including radiation sickness and depression of the blood-forming functions of the bone marrow) of this form of treatment have been explained to me to my satisfaction.

6. Any diagnostic study involving the use of radiomaterial:

The nature of the procedure to be performed and the meaning of the work "radioactive" have been explained to me to my satisfaction.

INFORMATION FOR PATIENTS RECEIVING RADIOIODINE

In order to study how your thyroid gland (goiter) is acting, we need to give you a small amount of radioiodine.

Radioiodine gives off radiations called beta rays and gamma rays. These rays are like x-rays and too many of them are harmful but thousands of people are examined by means of x-rays every day with no harmful effects. To the best of our knowledge, the amount of radiation you will receive will do you no harm.

We want you to understand that you are receiving small quantities of radiation after you drink the solution of radioiodine and ask you to sign that you have read and understand this brief statement.

DO NOT SIGN THIS IF YOU ARE PREGNANT.

Signature_____

Date _____

_____MD

_____MD

Print forms

INFORMATION FOR PATIENTS RECEIVING RADIO-IODINE

In order to treat the disease of your thyroid gland, we want to give you radio-iodine. Radio-iodine gives off beta and gamma rays while in your body - mostly in the thyroid gland. Beta and gamma rays act on the body much like x-rays. X-rays have been used for treatment of certain thyroid diseases for many years. While the use of radio-iodine is still experimental, we believe it will be more satisfactory than x-rays.

We want you to know that you are receiving radio-iodine when you drink the solution given you and to show that you have read and understood this simple statement please sign below.

Signature.....

Date.....

.....

..... MD

STANDARD FORM NO. 64

Office Memorandum • UNITED STATES GOVERNMENT

TO : Chief, Medical Plans and Operations Division
Chief, Legal Office
IN TURN

DATE: 3 August 1955

FROM : Chief, Medical Statistics Division

SUBJECT: Permit for Radioisotope Therapy

1. Reference is made to attached letter from Colonel Wells, Chief, Radiological Service, Letterman Army Hospital, concerning the desirability of obtaining an authorization for radioisotope therapy from the patient concerned; to memorandum, Chief, Medical Plans and Operations Division to Chief, Legal Office, 8 April 1955, subject as above; and to memorandum, Chief Legal Office to this division, 20 July 1955, subject as above.

2. It is the opinion of this division that Standard Form 522, Clinical Record—Authorization for Administration of Anesthesia and Performance of Operations and Other Procedures, is adequate for use in those instances when authorization for administration of radioisotope therapy is desired. It is suggested that signature by a patient of an authorization form which lists possible side effects or undesired results of such therapy may not relieve a hospital or physician of professional or legal responsibility. This division agrees with the view expressed by Medical Plans and Operations Division that the development of a special authorization form for one procedure may imply a requirement for such forms for other procedures, such as the administration of nitrogen mustard, of which issue and use is also controlled under SR 52-10-10.

Eugene L. Hamilton
EUGENE L. HAMILTON

Incl n/c

MEDDD-HO
NO. 2

DATE: 5 August 1955
Capt Holbrook/62840/mf

TO: Chief, Legal Office
Chief, Medical Statistics Division
IN TURN

FROM: Chief, Medical Plans and Operations Division

This division concurs in the above-comments of the Medical Statistics Division.

By Direction of Col MSC
THOMAS N. PAGE
Colonel, M. C.

1 Incl
n/c

DOE-0117-94-44

HUMAN STUDIES PROJECT TEAM	June 2, 1994
LOS ALAMOS NATIONAL LABORATORY	HSPT-REL-94-566
	Barcode: 00131775

Shipman, Thomas, L.
Letter to Dr. Charles L. Dunham
June 18, 1956

June 18, 1956

Dr. Charles L. Dunham
Division of Biology and Medicine
U. S. Atomic Energy Commission
Washington 25, D. C.

Dear Chuck:

Two questions have recently arisen -- one of them specific, the other general -- wherein we need an opinion from you. The first of these concerns making reproductions of the Los Alamos Monitors' Handbook, LA-1835, several copies of which should be floating around your Division. This little booklet has certainly been at the top of the best-seller list among Los Alamos documents and the demand shows no sign of slackening. We recently received a request for 100 copies from the Army Chemical Center at Ft. Belvoir. I would guess that somewhere between 1000 and 1500 copies have so far been distributed outside of Los Alamos. We are willing to continue reproducing and distributing this document for free unless someone else would like to take it over. We make no apologies for the fact that this document was prepared for our own Los Alamos monitors; it seems to be extremely popular elsewhere in spite of the fact that we did not hesitate to include some items which might be regarded as slightly controversial. If DBM wishes to authorize the reproduction and sale of this document from the GPO, we will be quite willing; otherwise, we will continue to distribute it at least to a limited degree essentially to those who request it.

That was the easy question and requires little more than a 'yes or no' answer from you. The next one is rather tougher. We feel that the time has come when it would be extremely helpful if DBM should restate its position on the matter of the experimental use of volunteer human subjects. To the best of my knowledge, Shields made such a statement some years ago; I think that this was before I joined the company and I don't believe that I ever saw it in black and white. People like laboratory directors, however, are aware of it and are understandably apprehensive when they learn or suspect that some of their workers are serving as guinea pigs.

I am bound to confess that we ourselves have from time to time indulged in experiments of this sort, most notably when we were studying the toxicity and toxicology of tritium. Furthermore, I am sure that you as a man with scientific training will agree that situations will arise when it becomes necessary to prove the validity of animal experiments with human administration. For your consideration I would like to suggest that you issue some sort of statement to

the effect that NIH does not object to the administration to human subjects of tracer doses of materials provided that a) the procedure is approved by the senior medical officer of the institution; b) that the subjects are bona fide volunteers and fully informed as to the procedure involved; and c) that the procedure be carried out under the supervision of a responsible physician who is licensed to practice in that locality.

In the absence of such a policy, such experiments will be carried on sub rosa anyway and possibly with inadequate supervision. My hope is for a reasonable policy which will permit people to do such work as is necessary and not keep us suffering from mistakes made in the distant past. Certainly your statement need not urge people to do these things but should at least withdraw the Division's disapproval.

Very sincerely yours,

THOMAS L. SHIPMAN, M. D.,
Health Division Leader

TLS/lcm

UNITED STATES
ATOMIC ENERGY COMMISSION
WASHINGTON 25, D. C.

IN REPLY REFER TO:

BM:CLD

July 5, 1956

Dr. Thomas H. Shipman
Los Alamos Scientific Laboratory
P. O. Box 1663
Los Alamos, New Mexico

Dear Tom:

This is in response to your letter of June 18. Question 1 is answered easily. The Los Alamos Monitors' Handbook is a little gen and when it is revised in the light of what would appear to be impending changes in the maximum permissible levels for external exposures I would hope that you could continue to make copies available as you have in the past. Although it might relieve you somewhat of the responsibility if it were published here under Division of Biology and Medicine auspices I can see two good reasons why this would not be desirable. One, it would require official endorsement by a number of interested Divisions which might delay its reproduction, and two, being a Los Alamos document rather than a government document it would, as has been demonstrated in the past, be much more acceptable and palatable. As to your second question, I fail to see any particular problem with respect to the administration of tracer doses of materials to human volunteers with four provisos: one, that these are true tracer doses and fall well below by an order of magnitude or two an amount which could result in something comparable to a continued maximum permissible body burden. The other three provisos are those you have suggested, namely, that the procedure be approved by a senior medical officer of the institution, that the subjects are bona fide volunteers and fully informed as to the procedure involved; and that the procedure be carried out under the supervision of a responsible physician who is licensed to practice in that locality. I think the context within which Shields made very strong statements decrying experimental use of volunteer human subjects was one in which there was tremendous pressure being put on both the AEC and the DOD to permit large doses of whole body radiation exposure in human volunteers, that is, hundreds of r to determine the dose levels at which nausea and vomiting would occur, impairment of work capacity and gross hematological change.

Sincerely yours,

Charles L. Dunham, M.D.
Director, Division of
Biology and Medicine

Shipman, Thomas L., MD
Memorandum to Distribution
July 12, 1956

TO : See Distribution July 12, 1946

FROM : T. L. Shipman, M. D., Health Division Leader

SUBJECT: ADMINISTRATION OF TRACER DOSES TO HUMANS

SYMBOL : H

Pursuing a suggestion made by Mr. Bradbury, I wrote to Dr. Dunham requesting from him a statement as to MED's feelings about the administration of tracer doses of isotopes to human volunteers. The following is his reply:

> "I fail to see any particular problem with respect to the administration of tracer doses of materials to human volunteers with four provisos: one, that these are true tracer doses and fall well below by an order of magnitude or two an amount which could result in something comparable to a confirmed maximum permissible body burden. The other three provisos are those you have suggested, namely, that the procedure be approved by a senior medical officer of the institution, that the subjects are bona fide volunteers and fully informed as to the procedure involved; and that the procedure be carried out under the supervision of a responsible physician who is licensed to practice in that locality."

Hereafter, these will be the guiding principles and the ordinary rules under which any such work will be carried out in Los Alamos. In order to reword these rules for local application, the following policy in regard to administration of tracer doses is hereby established:

1. Each experiment which requires the administration of tracer doses to human volunteers must have the written approval of the Health Division Leader or his Alternate.

2. The request for such approval must contain a statement as to the maximum dose to be administered, together with a statement as to the maximum permissible dose for such material.

3. All subjects will be bona fide volunteers who are fully informed as to the procedure to be carried out.

4. The administration of any such doses shall be carried out only under the immediate and direct supervision of a physician licensed to practice medicine in the State of New Mexico.

T. L. SHIPMAN, M. D.,
Health Division Leader

Distribution:
H-Div. Group Leaders
H-4 Section Leaders
L. E. Bradbury
Jane Hall
C. Dunham, MED
File

NARA-012395-A

School of Medicine
NEW ORLEANS 12, LA.

Department of
Tropical Medicine and Public Health
1430 Tulane Avenue

June 27, 1956

Captain R. W. Babione
MC, USN
Executive Secretary
Armed Forces Epidemiological Board
Office of the Surgeon General
Washington 25, D. C.

Dear Captain Babione:

Finally, I am able to complete and send to you the application for a research contract to study serum B vaccine modified for resubmission in accordance with suggestions made by the AFEB and transmitted verbally to me by Dr. Snyder.

I have held it up since Dr. Dingle indicated that I be familiar with the statement of the Office of the Surgeon General re the use of human volunteers. A copy of this statement finally reached me only last week. Needless to say, I have read it and believe that our past and future work have and will comply with the rules stipulated.

I understand that this modified application is to be circulated to the members of the AFEB so that I can expect to hear reasonably soon as to action taken.

Sincerely yours,

John F. Fox, M.D.
Professor of Epidemiology

JFF:fc

June Board, 1956
of BE

COPIED: 12/15/14
RECORD GROUP: 338
ENTRY: 14
FILE: (in box 14)

Supplemental statement to support application for a [redacted] further strain E typhus vaccine, originally submitted as of January [redacted] and in revised form as of June 22, 1956.

This statement is intended to answer certain questions regarding the application which were raised by members of the Armed Forces Epidemiological Board and transmitted to Dr. Fox by Dr. John C. Snyder by phone on September 17, 1956.

1. Concerning compliance with the principles, policies and rules of the Surgeon General concerning the use of human volunteers:

a. Re the sections dealing with voluntary consent, i.e., nos. 1, 2, 3 and 12, there is no problem insofar as civilian volunteers are concerned. The problem with respect to prisoner volunteers stems simply from the fact that they are prisoners and is more apparent than real, i.e. their being prisoners may be construed by some to limit their freedom of choice. In point of fact, at both Angola (La.) and Parchman (Miss.) a clear condition for our work on the part of the warden or superintendent is that the men must freely volunteer and, to insure that, we can offer them no inducement, financial or promise of time off, to obtain their consent. We do have permission to distribute cigarettes on occasion as a minor reward but never promised. Every reasonable effort is made to insure that the prospective volunteers understand the nature of the project and any risks or inconveniences related to their participation. This is done verbally in talking to small groups in which every opportunity for questions is given and, in less detail, in writing by incorporating a statement of the objectives and risk involved in the release forms. All volunteers are required to sign such forms in the presence of at least 2 witnesses, signing after each paragraph to indicate their having read and understood the paragraph and, finally, to indicate their free consent. Further, once in the study, the volunteer is free to drop out at any stage; in fact, not a few have done so in the past.

b. Concerning justification of the experiments conducted, i.e. section nos. 4-9 and 15, the Board must form its own opinion but the principal investigator believes that the risk with strain E vaccine is now known to be negligible, that the further work necessary can be done only in man, that previous animal experimentation provides a reasonable basis for the work, and that the proposed work inherently involves little occasion for physical and mental suffering or injury. The most consequential aspect is the matter of challenge with virulent typhus rickettsiae which is essential to establishing the effectiveness of the vaccine and which necessarily involves the use of non-immune volunteers as controls. The possible nature of the resulting disease is fully explained to the men who must re-volunteer at this stage. Adequate therapy, of course, is available and instituted as soon as the fact of disease is reasonably evident, i.e. after 48 hours of fever.

c. Medically speaking, relating to sections 10 and 11, the past and current health status including known allergies is considered before final entrance of the volunteer into the study and adrenalin is always at hand to cope with unexpected shock reactions to inoculation (not so far encountered in this work). At both Angola and Parchman very adequate hospital facilities exist and both prisons have had one (two at Parchman) physician in residence. However, at Angola from last January until now there has been no full time physician in spite of strenuous and continuing efforts to employ one. Personnel of the "medical corpsman" type are there, a Baton Rouge physician has visited regularly 3 times a week and was on constant call (he could be there within 1-2 hours), and we likewise have been and are on call with a 3-4 hr. travel time involved. Currently, it is reported that a full-time resident physician has just been employed again

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RECORD GROUP: 334
ENTRY: 14
FILE: (in box 74)

but the turnover in the job must be borne in mind. Volunteers who have been challenged usually have been retained in the hospital for a 21-day period from the time of challenge to permit closer supervision; in a few cases at Terchman (no challenges have yet been done at Angola) men at their own request have been permitted to remain in camp but with a regular regime of temperature taking and transfer to the hospital at the first sign of fever. At Terchman the prison physicians cared for the men who became ill on the basis of previous detailed instructions and frequent phone consultations with us in New Orleans. Unless a physician is available at Angola, a physician from our group will be stationed there during the anticipated period of illness resulting from challenge.

d. Other sections not specifically touched upon are nos. 13 and 14. Obviously, section 13 will be fully complied with; vaccination inoculations and/or challenge inocula will not be given to anyone who may have reacted adversely to a previous inoculum or whose current state of health may contra-indicate it. While it is hard to visualize any possible reason emerging in the light of our present knowledge, we also are prepared to halt the general program if indicated. Section 14, re prisoners of war, is not applicable.

2. Request for an advance protocol of a proposed experiment: It is felt that the plan of work is reasonably outlined on p. 4 of the revised application. However, to illustrate this point further, the plans for our next visit to Angola are indicated briefly below. Titrations for infectivity and bacteriologic safety tests for a new small lot of vaccine have just been completed. We plan now to titrate this lot in volunteers using 6 to 8 men per half-log dilution over a 5 dilution range which we expect will bracket the infectivity end-point in man as determined by serologic response. This experiment has been done twice before and will be repeated a number of times in the future using different lots of vaccine or the same lot after periods of storage in order to define more certainly the relation between vaccine infectivity as measured in eggs before and after lyophilization and immunizing potency in man. An added objective is to verify our assumption that the delayed type of reactions can be controlled by appropriate antibiotic therapy. For this reason the occurrence of such reactions will be sought and, using temperature of 100° F. as an objective criterion, alternate instances of reaction will be treated or given a placebo. Because of the low incidence of such reactions this procedure will be part of each individual experiment, thus permitting slow cumulation of pertinent data. Men known to have become immune during these titration experiments will provide a pool from which candidates for future challenge experiments or efforts to induce recrudescent infection will be recruited.

3. Concerning the need for the funds requested and the relation of the requested AFEB support to support for similar work by the USPHS: Apparently this question arises in part from the final sentence on p. 4 of the revised request which reads "The foregoing work is being initiated with current USPHS support but will certainly extend well beyond the time of termination of the present grant." When that sentence was written, current grant June, 1956, and the time of termination meant August 31, 1956. Since then, a pending USPHS grant has been finally approved and paid, ostensibly to support the same work proposed under the AFEB request plus the Peruvian work originally proposed but since deleted from the AFEB request. As explained in a letter dated August 4, 1956, to Dr. Snyder and intended for any necessary circulation, the intention was to accept the AFEB contract if approved and to discuss with Dr. Karel the possibility of using a portion of the USPHS funds to terminate the Peruvian work. Preference for the AFEB congract derived chiefly from the fact that the budget requested had been prepared considerably later than that requested of the USPHS (after considerable re-thinking of the program) and provided for somewhat more technical help and supplies. It also provided for the entire salary of Dr. Jordan, who spends her full time on the

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RECORD GROUP: 334
ENTRY: 14
FILE: (in box)

syphus work, a point of some importance since funds for the major portion of her salary, now derived from the rather meager Departmental budget, would become available to help obtain some badly needed teaching assistance.

4. Concerning the effective date of the contract: September 1, 1956, was set originally in the expectation that the contract would replace essentially the USPHS grant which terminated on August 31. That date having already passed, January 1, 1957, is suggested as a convenient new date to allow time for any further processing of this request and to arrange for the disposition of the unexpended part of the current new USPHS grant.

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ENTRY: #14
FILE: (in box #)

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X

June 18, 1956

Dr. Charles L. Dunham
Division of Biology and Medicine
U. S. Atomic Energy Commission
Washington 25, D. C.

Dear Chuck:

Two questions have recently arisen -- one of them specific, the other general -- wherein we need an opinion from you. The first of these concerns making reproductions of the Los Alamos Monitors' Handbook, LA-1835, several copies of which should be floating around your Division. This little booklet has certainly been at the top of the best-seller list among Los Alamos documents and the demand shows no sign of slackening. We recently received a request for 100 copies from the Army Chemical Center at Ft. Belvoir. I would guess that somewhere between 1000 and 1500 copies have so far been distributed outside of Los Alamos. We are willing to continue reproducing and distributing this document for free unless someone else would like to take it over. We make no apologies for the fact that this document was prepared for our own Los Alamos monitors; it seems to be extremely popular elsewhere in spite of the fact that we did not hesitate to include some items which might be regarded as slightly controversial. If DBM wishes to authorize the reproduction and sale of this document from the GPO, we will be quite willing; otherwise, we will continue to distribute it at least to a limited degree essentially to those who request it.

That was the easy question and requires little more than a 'yes or no' answer from you. The next one is rather tougher. We feel that the time has come when it would be extremely helpful if DBM should restate its position on the matter of the experimental use of volunteer human subjects. To the best of my knowledge, Shields made such a statement some years ago; I think that this was before I joined the company and I don't believe that I ever saw it in black and white. People like laboratory directors, however, are aware of it and are understandably apprehensive when they learn or suspect that some of their workers are serving as guinea pigs.

I am bound to confess that we ourselves have from time to time indulged in experiments of this sort, most notably when we were studying the toxicity and toxicology of tritium. Furthermore, I am sure that you as a man with scientific training will agree that situations will arise when it becomes necessary to prove the validity of animal experiments with human administration. For your consideration I would like to suggest that you issue some sort of statement to

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the effect that DRM does not object to the administration to human subjects of tracer doses of materials provided that a) the procedure is approved by the senior medical officer of the institution; b) that the subjects are bona fide volunteers and fully informed as to the procedure involved; and c) that the procedure be carried out under the supervision of a responsible physician who is licensed to practice in that locality.

In the absence of such a policy, such experiments will be carried on sub rosa anyway and possibly with inadequate supervision. My hope is for a reasonable policy which will permit people to do such work as is necessary and not keep us suffering from mistakes made in the distant past. Certainly your statement need not urge people to do these things but should at least withdraw the Division's disapproval.

Very sincerely yours,

THOMAS L. SHIPMAN, M. D.,
Health Division Leader

TLS/lcm

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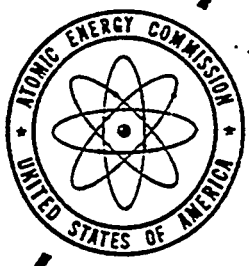
THE MEDICAL USE OF RADIOISOTOPES

RECOMMENDATIONS AND REQUIREMENTS BY THE ATOMIC ENERGY COMMISSION



Isotopes Extension
Division of Civilian Application
U. S. Atomic Energy Commission
Oak Ridge, Tennessee
February 1956

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THE MEDICAL USE OF RADIOISOTOPES

RECOMMENDATIONS AND REQUIREMENTS BY THE ATOMIC ENERGY COMMISSION

I. INTRODUCTION

The present procedures of the Atomic Energy Commission for the allocation of radioisotopes for medical research, diagnosis and therapy are set forth in this announcement. The recommendations for minimum clinical radioisotope training and experience for use of radioisotopes in human subjects have been established in advisement with the Subcommittee on Human Applications of the Atomic Energy Commission's General Advisory Committee on Isotope Distribution.

These recommendations are designed to provide guidelines for physicians and typify the nature rather than the precise extent of the desirable clinical radioisotope experience. For special situations, other experience may serve in lieu of the particular recommendations set forth in this announcement.

II. ADMINISTRATIVE PROCEDURE FOR RADIOISOTOPE PROCUREMENT

A. Application

A medical institution or a physician in an individual medical practice desiring to obtain radioisotopes, forwards to the Isotopes Extension*, Form AEC-313, "Application for Byproduct Material Licenses," and Supplement A, (Form AEC-313-a). If the radioisotopes are to be obtained as sealed sources (such as Cobalt 60 for teletherapy units or Strontium 90 for medical eye applicator) the applicant should complete the basic form (Form AEC-313) and Supplement B (Form AEC-313-b). These forms should be completed in accordance with the instructions attached thereto. Applications for use of radioisotopes in human subjects in an INSTITUTIONAL MEDICAL PROGRAM should be supported by the special information described under Section III, Page 4, Section IV, Page 6 and Section V, Page 8 of this announcement for such use by a physician in his INDIVIDUAL MEDICAL PRACTICE the application should be supported by the special information described under Section III, Page 4, Section VI, Page 15 and Section VII, Page 18.

In considering such applications, the Atomic Energy Commission is concerned primarily with matters of radiological health safety. Toward this end the Commission seeks to determine if the applicant has equipment and facilities appropriate to the proposed use and whether the physician is trained in basic principles of radioactivity and has specific experience in the use of radioisotopes in the clinical situations being proposed. The information is indicated by the applicant on his application form and the supplementary sheets attached thereto.

* Allocations Branch, Isotopes Extension, Division of Civilian Application U. S. Atomic Energy Commission, P. O. Box E, Oak Ridge, Tennessee.

B. License

Upon favorable review of the application (See NOTE below), Form AEC-374, "Byproduct Material License," is issued. This license permits the holder to procure radioisotopes in accordance with the conditions stated on the application and license forms and in Title 10 of the Code of Federal Regulations.

NOTE: The Isotopes Extension normally reviews applications proposing new or nonroutine medical uses of radioisotopes in collaboration with the Advisory Subcommittee on Human Applications. This review usually requires four weeks for completion.

C. Types of Clinical Radioisotope Programs

The recommendations and requirements established by the Atomic Energy Commission for the clinical use of radioisotopes are designed to provide for two types of medical radioisotope programs. These are defined as follows:

1. Institutional Medical Radioisotope Program

Clinical radioisotope programs established by a medical institution and carried out under the guidance of a medical isotopes committee (See recommendations for membership and duties of a medical isotopes committee in Section IV, A. Page 6) are designated as "Institutional use". Licenses for institutional use require that the physician(s) named on the license form supervise the conduct of the program with the guidance of the medical isotopes committee. The use of the radioisotope(s) shall be by, or in the presence of or under the supervision of, the physician(s) indicated on the license and confined to the location and the purposes indicated thereon.

NOTE 1: Physicians other than those named on the license form may participate in the medical radioisotopes program with the general supervision of the named physicians and upon approval by the medical isotopes committee. Institutional type programs provide a vehicle whereby physicians other than those named on an AEC license may have an opportunity to gain radioisotope experience commensurate with the recommendations in this announcement. Such experience may assist these physicians in initiating a medical program at other institutions or in their individual practice.

NOTE 2: Individual physicians within an institutional medical program operated under the guidance of a medical isotopes committee are discouraged from initiating separate applications for use of radioisotopes in specific clinical programs where the institution already holds a license (Form AEC-374) for such use. It is recommended that one or more physicians experienced in the use of a radioisotope for a particular clinical situation be designated by the medical isotopes committee as the nominally responsible physician(s) on the application for radioisotopes. Subject to the approval of the medical isotopes committee other staff physicians may administer radioisotopes to patients in consultation with or under the supervision of the physician(s) designated on the license form as mentioned in NOTE 1 above.

2. Individual Practice Medical Program

Medical radioisotope programs which are to be conducted by a physician in his individual practice without the guidance of a medical isotopes committee are designated as "individual practice use". These programs are limited to

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well-established medical uses of radioisotopes. Licenses for the use of radioisotopes in individual practice require that the physician(s) so licensed personally carry out the program. Such use shall be confined to the location, dosage and purposes indicated on the license form.

D. Supporting Information to Accompany Application

1. Applications for "institutional use" should provide the supporting information described in Sections III, IV and V of this announcement.

2. Applications for "individual practice use" should provide the supporting information described in Sections III, VI and VII.

III. GENERAL REQUIREMENTS FOR MEDICAL USE OF RADIOISOTOPES

A. Preceptor Statement

A standard preceptor form has been prepared by the Isotopes Extension as a convenient means of furnishing information concerning the physician's basic radioisotope training and clinical experience in the use of radioisotopes. The physician should have his medical preceptor in the clinical radioisotope work proposed forward a completed "Preceptor Statement" to the Isotopes Extension with his initial applications. When a physician wishes to extend his program to include other clinical situations a new preceptor form normally should be submitted if information concerning his experience in these medical uses has not previously been provided.

B. Dosage Schedule

Every application shall include the proposed dosage range for each of the diseases or conditions to be followed. When the isotope is proposed for both diagnosis and therapy, the dosage range for each is to be stated separately. The approximate dosage (in millicuries or microcuries) per single administration is to be indicated as well as the number and frequency of such doses.

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Applications proposing such experimental or nonroutine uses of radioisotopes in human subjects should be supported by a statement detailing the rationale for the dosage proposed and other data as set forth under Section V.E., Page 14.

C. Prerequisites for Use

1. The individual to use radioisotopes in human subjects shall be a physician licensed to dispense drugs in the practice of medicine by a state or territory of the United States, the District of Columbia or the Commonwealth of Puerto Rico.

2. Normally the proposal to use radioisotopes in human subjects should be appropriate to the scope of the physician's medical experience, specialty and/or board certification.

3. The physician should have personal experience gained through "basic radioisotope training" and "active participation" as defined in Part (a) and (b) below. The active participation shall be obtained by collaborating in a program using radioisotopes in clinical situations comparable to those proposed in the application. The training and experience should be in accordance with the recommendations cited under Sections V, or VII, "Recommendations for MINIMUM Clinical Radioisotope Experience for use of Radioisotopes."

   a. Basic radioisotope training* shall provide the physician a working knowledge of

      1. Principles and practices of radiological health safety.

      2. Radioactivity measurement standardization and monitoring techniques and instruments.

      3. Mathematics and calculations basic to the use and measurement of radioactivity.

      4. Biological effects of radiation.

      5. Actual use of radioisotopes in the types and quantities for which application is being made, or equivalent experience.

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* Satisfactory completion of the Oak Ridge Institute of Nuclear Studies "Basic Course in Techniques Using Radioisotopes" or its equivalent will serve as evidence of compliance with requirements in basic training.

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B. Active Participation Consists of:

1. Evaluation of the suitability of the patient for radioisotope diagnosis and/or treatment by taking patient histories and performing medical examinations and/or study of case histories.

2. Collaboration in diagnosis and/or treatment and dosages prescribed.

3. Measurement of doses and their administration.

4. Related measurements and plotting of data.

5. Active period of training and experience of sufficient duration to permit the following of specific patients through treatment and post-treatment periods, including reevaluation as to effectiveness and complications.

6. Study of case histories (without seeing patients).

7. Study of case histories (observed patients).

8. Observation and discussion of diagnostic and/or therapeutic techniques, as well as management of patients during follow-up periods.

NOTE: Details of the physicians active participation should be indicated by his medical preceptor on the standard preceptor form discussed in Section III A, page 4.

IV. SPECIAL REQUIREMENTS FOR INSTITUTIONAL MEDICAL PROGRAM
(See also General Requirements cited under Section III, above)

A. Medical Isotopes Committee

The applicant institution shall appoint a medical isotopes committee to evaluate all proposals for research, diagnostic and therapeutic use of radioisotopes within the institution. The initial application from an institution should include the names, specialties, and pertinent radioisotope experience, if any, of the members of the medical isotopes committee. The functions of the committee, as well as the administrative procedures by which it carries out these functions, should also be defined. In subsequent applications any changes in the membership of the committee should be described.

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NOTE: Where the use of radioisotopes in a medical institution is to be limited to sealed radiation sources for well established intracavitary, interstitial or external therapeutic procedures, a medical isotopes committee is not necessary. See Section VIII, Page 23.

1. Formation of a Medical Isotopes Committee

The Medical Isotope Committee shall include at least three members. Membership should include physicians expert in internal medicine (or hematology), pathology, or therapeutic radiology and a person experienced in assay of radioisotopes and protection against ionizing radiations. It is often appropriate that a qualified physicist be available to the Committee, at least in a consulting capacity.

It is recognized that the composition of local isotopes committees may vary from institution to institution depending upon the individual interests of a particular medical facility.

2. Duties of the Medical Isotopes Committee

Generally, the Committee should have the following responsibilities:

a. Review and grant permission for, or disapprove, the use of radioisotopes within the institution from the standpoint of radiological health safety and other factors which the Committee may wish to establish for medical use of these materials.

b. Prescribe special conditions which may be necessary, such as physical examinations, additional training, designation of limited area or location of use, disposal methods, etc.

c. Review records and receive reports from the radiological safety officer or other individual responsible for health-safety practices.

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d. Recommend remedial action when a person fails to observe safety recommendations and rules.

e. Keep a record of actions taken by the Committee.

B. Radioactive Pharmaceuticals

Radiomaterials distributed by Atomic Energy Commission-owned laboratories are not necessarily of pharmaceutical quality and are not warranted as to identity, quality or quantity. An applicant desiring to procure radiomaterials for human use, therefore, must either purchase them preassayed and of pharmaceutical quality from commercial concerns or process them himself should he choose to receive these materials from Commission laboratories. Where the latter option is chosen, the applicant should include with his application the following information:

1. His experience in standardization and measurement techniques.

2. The procedures to be employed for identifying and assaying the radiomaterial and carrying out such other testing and processing (sterilization, pyrogen tests, etc.) as may be appropriate.

3. The instruments and equipment available for this purpose.

NOTE: When purchasing radiomaterials from an AEC distributor (e.g. Oak Ridge National Laboratory), all non-federal applicants must use a special "Isotope and Service Irradiation Order Form" (Form AEC-391) and federal agencies must use an "Isotope Order Blank" (Form AEC-375). Copies of these forms are available from the AEC distributors and Isotopes Extension. These forms are not intended for use when ordering materials from other than AEC distributors.

V. RECOMMENDATIONS FOR MINIMUM CLINICAL RADIOISOTOPE EXPERIENCE FOR INSTITUTIONAL USE (In addition to the requirements discussed in Section III C., Page 5, the physician should have clinical radioisotope experience commensurate with the following recommendation(s) applicable to the use(s) proposed on his application.

A. Iodine 131

1. Diagnosis of Thyroid Function

The physician should work for at least 30 hours in a medical program where Iodine 131 for diagnosis of thyroid function and treatment of thyroid disease is being used.

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During the 30-hour period of time the physician should actively participate in such diagnostic studies in at least 10 patients.

NOTE: The Iodine 131 unless otherwise exempted, shall be procured in precisely calibrated form.

2. Determination of Blood Volume and Plasma Volume

The physician should work for at least 30 hours in a medical program where Iodine 131 for blood determinations is being used.

During the 30-hour period of time the physician should actively participate in 10 such blood determinations.

Physicians already using Iodine 131 in diagnosis of thyroid function can qualify after active participation in 3 such blood determinations.

NOTE: The Iodine 131 unless otherwise exempted shall be procured in a sterilized, precisely calibrated form.

3. Diagnosis of other Clinical Conditions

The use of Iodine 131 for the localization of brain tumors, hepatic malignancies, etc., represents specialized applications requiring considerable refinement in techniques and specialized instrumentation. The use of radioiodine for these purposes is normally limited to physicians already having substantial experience in both diagnostic and therapeutic use of radioisotopes as well as specific experience in the modality being proposed.

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Applications proposing such use of radioisotopes should be supported with information describing the clinical procedures to be followed and the instrumentation to be used.

4. Treatment of Hyperthyroidism and/or Cardiac Dysfunction

The physician should actively participate in the use of Iodine 131 for the treatment of hyperthyroidism and/or cardiac dysfunction in a minimum of 10 patients.

5. Treatment of Thyroid Cancer

The physician should have (1) experience as set forth in 4 above and (2) active participation in the use of Iodine 131 for the treatment of thyroid cancer in a minimum of 3 patients.

B. Phosphorus 32

1. Diagnosis

The use of Phosphorus 32 for localization of brain tumors, eye tumors, etc., represents specialized applications of radioisotopes requiring considerable refinement in techniques and specialized types of instrumentation. The use of radiophosphorus for these purposes is normally limited to physicians already having substantial experience in both diagnostic and therapeutic use of radioisotopes, as well as specific experience in the modalities being proposed.

Applications proposing such use of radioisotopes should be supported with information describing the clinical procedures to be followed and the instrumentation to be used.

2. Treatment of Leukemia, Polycythemia and Allied Blood Dyscrasias

a. The physician should be expert in therapeutic radiology, internal medicine (or hematology) or pathology. Board certification will serve as evidence of qualifications.

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b. Physicians who are not qualified as indicated above should actively participate in the use of Phosphorus 32 for the treatment of leukemia, polycythemia vera and/or other blood dyscrasias in a minimum of 5 patients.

3. Phosphorus 32 - Chromic Phosphate

a. Intracavity Use in the Palliation of Carcinomatous Patients

(1) The physician should actively participate in the use of Phosphorus 32-labeled chromic phosphate in the treatment of a minimum of 5 carcinomatous patients.

(2) Experience in the intracavity use of colloidal Gold 198 will serve in lieu of the recommendations set forth in (1) above.

NOTE: Applications proposing the intracavity use of Phosphorus 32-labeled chromic phosphate should be accompanied by a properly annotated drawing of the infusion apparatus to be used or a literature reference to such apparatus.

b. Interstitial Use in the Treatment of Prostatic and/or Cervical Cancer

(1) The interstitial use of Phosphorus 32-labeled chromic phosphate for treatment of prostatic and/or cervical cancer entails a specialized procedure. Such therapy, therefore, should usually be carried out by a team which includes a surgeon of appropriate specialty and a therapeutic radiologist both of whom are experienced in this modality. The surgeon should actively participate in the treatment of 6 to 8 patients and the therapeutic radiologist in the planning for and handling of 1 to 2 patients.

(2) Experience in the interstitial use of colloidal Gold 198 for prostatic and/or cervical cancer will serve in lieu of the recommendation set forth in (1) above.

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NOTE 1: The use of Phorphorus 32-labeled chromic phosphate interstitially in the treatment of prostatic cancer and/or cervical cancer is not considered to be routine. Therefore, applications proposing this therapy should be submitted as an investigative program which outlines in detail the study conditions to be evaluated.

NOTE 2: Applications proposing the interstitial use of Phosphorus 32-labeled chromic phosphate should be accompanied by a properly annotated drawing of the injection apparatus or a literature reference to such apparatus.

C. Gold 198 Colloid

1. Intracavity Use for Palliation of Carcinomatous Patients

a. Physicians who have personal experience in the actual handling of equivalent amounts of other gamma emitting radioisotopes, e.g., Iodine 131 for the treatment of thyroid carcinoma, should actively participate in the treatment of a minimum of 2 to 3 carcinomatous patients.

b. Physicians without personal experience in the actual handling of equivalent amounts of other gamma emitters should actively participate in the use of Gold 198 colloid in the treatment of a minimum of 5 carcinomatous patients.

NOTE 1: Applications proposing the intracavity use of Gold 198 colloid should be accompanied by a properly annotated drawing of the infusion apparatus to be used or a literature reference to such apparatus.

NOTE 2: Because of the magnitude of the dose of Gold 198 colloid used for palliation of carcinomatous patients and the accompanying gamma ray flux, the application should be accompanied by a detailed discussion of the special instructions to be given hospital personnel concerning the care and handling of such patients and the special radiological health safety procedures to be followed.

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NOTE 3: The application should state whether the Gold 198 colloid will be obtained from the supplier in individually prepared doses or whether patient doses will be prepared by the physician from stock solution. If the latter is the case specific details should be presented concerning assay and safe handling procedures.

2. Interstitial Use for Treatment of Prostatic and/or Cervical Cancer

The interstitial use of Gold 198 colloid for treatment of prostatic and/or cervical cancer entails a specialized procedure. Therefore, such therapy should usually be carried out by a team which includes a surgeon of appropriate specialty and a therapeutic radiologist both of whom are experienced in this modality. The surgeon should actively participate in the treatment of 6 to 8 patients and the therapeutic radiologist in the planning for and handling of 1 to 2 patients.

NOTE 1: Applications proposing the interstitial use of Gold 198 colloid should be accompanied by a properly annotated drawing of the injection apparatus to be used or a literature reference to such apparatus.

NOTE 2: Because of the magnitude of the dose of Gold 198 colloid used for interstitial therapy of cancer patients and the accompanying gamma flux the application should be accompanied by a detailed discussion of the special instructions to be given hospital personnel concerning the care and handling of such patients and the special radiological health safety procedures to be followed.

NOTE 3: The application should state whether the Gold 198 colloid will be obtained from the supplier in individually prepared doses or whether patient doses will be prepared by the physician from a stock solution. If the latter is the case specific details should be presented concerning assay and safe handling procedures.

D. Chromium 51

Determination of Blood Volume, Plasma Volume and Erythrocyte Survival

1. The physician should work for at least 30 hours in a medical program where Chromium 51 for blood determinations

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is being used.

During the 30 hour period of time the physician should actively participate in 10 such blood determinations.

NOTE: The Chromium 51, unless otherwise exempted, shall be procured in a sterilized, precisely calibrated form.

2. Physicians trained in the use of other radioisotopes for diagnostic and therapeutic purposes can qualify after active participation in 3 such blood determinations.

E. Experimental or Nonroutine Use of Radioisotopes in Human Subjects

The experimental use of radioisotopes in human subjects, whether for research, diagnostic or therapeutic purposes shall be limited to physicians with broad radioisotope experience and to institutional type programs.

Applications proposing the experimental use of radioisotopes in human subjects should be supported with a detailed proposal outlining the study conditions to be evaluated. Preferably this type of program should be preceded by studies in animals which have established the assimilation, distribution, selective localization and excretion of the radioisotope in question (or its derivatives) sufficiently well to permit extrapolation to man for dosage purposes. These animal data should be included as part of the application.

In the absence of animal data the proposal should include detailed remarks concerning the rationale for the dose to be used.

Ordinarily, radioisotopes with half-lives greater than 30 days will not be available for internal use in human subjects unless prior studies on animals have established the metabolic properties noted above. It is recognized, however, that special circumstances may arise which indicate the desirability or necessity for the use of long-lived radioisotopes in human subjects where prior animal data are not available. Consideration of such proposals shall be limited to patients suffering from diseased conditions of such a nature (life expectancy of one year or less) that there is no reasonable probability of the radioactivity employed producing manifest injury.

NOTE 1: To assist the Atomic Energy Commission and its Subcommittee on Human Applications in considering like proposals from other groups, it is requested that data obtained in the experimental or nonroutine use of radioisotopes be forwarded to the Isotopes Extension.

2002510

NOTE 2: Use of radioisotopes in normal subjects for experimental purposes shall be limited to:

a. Tracer doses which do not exceed the permissible total body burden for the radioisotope in question. In all instances the dose should be kept as low as possible.

b. Volunteers to whom the intent of the study and the effects of radiation have been outlined.

c. Volunteers who are unlikely to be exposed to significant additional amounts of radiation.

NORMALLY EXCLUDES:

(1) Infants and pregnant women.

(2) Use of the same volunteers for a long series of studies.

VI. SPECIAL REQUIREMENTS FOR THE INDIVIDUAL PRACTICE MEDICAL PROGRAM (In addition to the General Requirements, cited under Section III, Page 4)

NOTE: A distinction is made between (1) individual medical practice programs confined primarily to the use of radioisotopes in the physician's private office and (2) individual medical practice programs confined to the use of radioisotopes within a medical facility.

A. Individual Medical Practice in the Physician's Office

1. Clinical Facilities

The application should state that the physician has access to a hospital possessing adequate facilities to hospitalize and monitor the physician's radioactive patients whenever hospitalization is advisable. This does not refer to the physician's staff privileges at an institution, but rather serves to indicate the institution's willingness to have radioactivity on its premises. From the standpoint of radiological safety alone it is advisable that patients with more than 30 millicuries of radioisotopes internally administered be hospitalized. It is strongly recommended that in all cases a patient containing more than 50 millicuries be hospitalized.

2002511

a. The application should set forth the following:

(1) Arrangements which have been made to provide each hospital with the necessary radiation protection instruments and other special equipment as well as instructions given to staff personnel for the care of radioactive patients to provide adequate radiological health safety.

(2) Arrangements for notification to hospital authorities of admission of a radioactive patient.

b. A statement should be obtained and retained by the physician from EACH hospital in which he has made arrangements to admit patients containing radioisotopes expressing the institution's willingness to hospitalize his radioisotope patients and acknowledging receipt of adequate radiological health safety instructions.

2. Radiological Health Safety Measures

The application should set forth the following:

a. Outline of a program to observe adequate health safety standards including adequate instrumentation, careful maintenance of case records and activity inventory with respect to isotope use and disposal.

b. A statement should be presented concerning arrangements that have been made with a readily available radiological safety consultant for both periodic and emergency visits if such services are to be used. Although the applicant physician must possess adequate background and experience in radioactivity to assure radiological safety, he may not wish to perform the duties of a radiological safety officer.

c. Provisions for adequate instrumentation for measurement as well as for maintenance of health and safety standards.

2002512

B. Individual Medical Practice in Hospitals

In some instances physicians using radioisotopes in their individual medical practice have found it convenient and/or desirable to carry out such use within a medical institution rather than at their private office. The responsibility for this type of use is solely that of the individual physician; the medical institution simply provides physical space for carrying out the program. This type of use of radioisotopes for medical purposes does not require that the program be carried out under the auspices of a medical isotopes committee.

If the applicant physician wishes to use radioisotopes in a hospital as discussed above, he should obtain and retain in his files a statement from the hospital administration expressing the institution's willingness for radioisotopes to be used within their facilities.

Applications for use of radioisotopes by a physician in his individual medical practice, but where such use is physicially located in a medical institution should be supported by the following information:

1. Arrangements made to provide the hospital with necessary radiation detection instruments and instructions to be given staff personnel for the care of radioactive patients whenever they are needed to provide adequate radiological health safety.

2. Arrangements for notification to the hospital authorities of admission of a radioactive patient or of a patient admitted for the administration of radioisotopes.

3. Arrangements made to provide for the receipt and safe storage of radioisotope shipments made to the hospital.

C. Radioactive Pharmaceuticals

Radiomaterials distributed by the Atomic Energy Commission owned laboratories are not necessarily of pharmaceutical quality and are not warranted as to identity, quality or quantity. It is usually desirable, therefore, that a physician using radioisotopes in his individual medical practice purchase them preassayed and of pharmaceutical quality.

If the physician in his individual medical practice wishes to obtain radioisotopes for human use from AEC laboratories he should include with his application the following information:

1. His experience in standardization and measurement techniques.

2. The procedures to be employed for identifying and assaying the radiomaterial and carrying out such other operations (sterilization, pyrogen tests, etc.) as may be appropriate.

NOTE: When purchasing radiomaterials from an AEC distributor (e.g. Oak Ridge National Laboratory), all non-federal applicants must use a special "Isotope and Service Irradiation Order Form" (Form AEC-391) and federal agencies must use an "Isotope Order Blank" (Form AEC-375). Copies of these forms are available from the AEC distributors and Isotopes Extension. These forms are not intended for use when ordering materials from other than AEC distributors.

VII. RECOMMENDATIONS FOR MINIMUM CLINICAL RADIOISOTOPE EXPERIENCE FOR INDIVIDUAL MEDICAL PRACTICE USE

(In addition to the requirements discussed in Section III C., Page 5, the physician should have clinical radioisotope experience commensurate with the following recommendation(s) applicable to the use(s) proposed on his application)

A. Iodine 131

1. Diagnosis of Thyroid Function

The physician should work for at least 30 hours in a medical program where Iodine 131 for diagnosis of thyroid function and treatment of thyroid disease is being used.

During the 30-hour period of time the physician should actively participate in such diagnostic studies in at least 10 patients.

NOTE: The Iodine 131, unless otherwise exempted, shall be procured in a precisely calibrated form.

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2. Determination of Blood Volume and Plasma Volume

a. The physician should work for at least 30 hours in a medical program where Iodine 131 for blood determinations is being used.

During the 30-hour period of time the physician should actively participate in 10 such blood determinations.

b. Physicians already using Iodine 131 in diagnosis of thyroid function can qualify after active participation in 3 such blood determinations.

NOTE: The Iodine 131, unless otherwise exempted, shall be procured in a sterilized and precisely calibrated form.

3. Treatment of Hyperthyroidism and/or Cardiac Dysfunction

The physician should associate himself directly with a medical group using Iodine 131 for treatment of hyperthyroidism and/or cardiac dysfunction for a period equivalent to a minimum of two months' full-time work. Participation during the two-month period need not be on a continuous basis but may be arranged on a schedule suited to the needs of the physician and his medical preceptor. During the period of training the physician should actively participate in the use of Iodine 131 for the treatment of hyperthyroidism and/or cardiac dysfunction in a minimum of 15 patients.

4. Treatment of Thyroid Cancer

The physician should have (1) experience as set forth in 3. above and (2) active participation in the use of Iodine 131 for the treatment of thyroid cancer in a minimum of 5 patients.

NOTE: Such therapy should normally be carried out in and the patient confined to a hospital or other medical institution having in-patient facilities and adequate radiation equipment to assure radiological health safety.

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B. Phosphorus 32

1. Treatment of Leukemia, Polycythemia and Allied Blood Dyscrasias

a. The applicant physician should be expert in therapeutic radiology, internal medicine (or hematology) or pathology (Board certification will serve as evidence of such qualification), who has actively participated in the use of Phosphorus 32 for the treatment of leukemia, polycythemia vera and/or other blood dyscrasias in a minimum of 5 patients.

b. Physicians who are not qualified as indicated above, should actively participate in the use of Phosphorus 32 for the treatment of leukemia, polycythemia vera and/or other blood dyscrasias in a minimum of 10 patients.

2. Phosphorus 32 - Chromic Phosphate

a. Intracavity Use in the Palliation of Carcinomatous Patients

The physician should have (1) substantial experience in the use of Phosphorus 32 as well as other radioisotopes for diagnostic and therapeutic purposes and (2) active participation in the use of P 32-labeled chromic phosphate for the treatment of a minimum of 10 carcinomatous patients.

NOTE 1: Since this therapy is not considered routine and the technique is normally a hospital procedure, the use of Phosphorus 32-labeled chromic phosphate shall be carried out in, and the patient confined to a hospital or other medical institution having in-patient facilities and adequate radiation equipment to assure radiological health safety.

NOTE 2: Applications proposing the intracavitary use of Phosphorus 32-labeled chromic phosphate should be accompanied by a properly annotated drawing of the infusion apparatus to be used or a literature reference to such apparatus.

2007516

NOTE 3: The application should clearly state whether the Phosphorus 32-labeled chromic phosphate will be obtained in individually prepared doses or whether such doses will be prepared by the physician from stock solution. If the latter is the case, specific details should be presented concerning assay and safe handling procedures.

b. Interstitial Use in the Treatment of Prostatic and/or Cervical Cancer

The interstitial use of Phosphorus 32-labeled chromic phosphate for treatment of prostatic and/or cervical cancer is normally limited to institutional medical radioisotope programs being conducted under the auspices of a medical isotopes committee. This limitation is made since the use of chromic phosphate interstitially is still considered to be investigative in nature. The use of radioisotopes by a physician in his individual medical practice is normally limited to well-established medical uses of radioisotopes.

C. Gold 198 Colloid

1. Intracavity Use for Palliation of Carcinomatous Patients

The physician shall have (1) substantial experience in the use of equivalent amounts of other gamma emitting radioisotopes for therapeutic purposes, e.g., Iodine 131 for the treatment of thyroid cancer and (2) active participation in the use of Gold 198 colloid for the treatment of a minimum of 10 carcinomatous patients.

NOTE 1: Because the use of Gold 198 colloid for the above purpose is normally a hospital procedure and the magnitude of the dose used results in a high gamma flux during and after instillation into the patient, this clinical application shall be carried out in and the patient confined to a hospital or other medical institution having in-patient facilities and adequate radiation equipment to assure radiological health safety.

NOTE 2: Applications proposing the intracavity use of Gold 198 colloid should be accompanied by a properly annotated drawing of the infusion apparatus to be used or a literature reference to such apparatus.

NOTE 3: The application should be accompanied by a detailed discussion of the special instructions to be given hospital personnel concerning the care and handling of such patients and the special radiological health safety procedures to be followed.

NOTE 4: The application should state whether the Gold 198 colloid will be obtained in individually prepared doses or whether such doses will be prepared by the physician from stock solution. If the latter is the case specific details should be presented concerning assay and handling procedures.

2. Interstitial Use for Treatment of Prostatic and/or Cervical Cancer

The interstitial use of Gold 198 colloid for the treatment of prostatic and/or cervical cancer is normally limited to the institutional medical radioisotope programs being conducted under the auspices of a medical isotopes committee. The limitation is made since the use of gold colloid interstitially is still considered to be investigative in nature. The use of radioisotopes by a physician in his individual medical practice is normally limited to well-established medical uses of radioisotopes.

D. Chromium 51

Determination of Blood Volume, Plasma Volume and Erythrocyte Survival

The physician should work for at least 30 hours in a medical program where Chromium 51 is being used for blood determinations.

During the 30-hour period of time the physician should actively participate in 10 such blood determinations.

2002518

VIII. DESIRABLE CLINICAL EXPERIENCE FOR MEDICAL USE OF SEALED RADIATION SOURCES

The recommendations for training and experience, as set forth below, for use of radioisotopes as sealed radiation sources for external, interstitial or intracavitary therapy are applicable to both institutional programs and individual medical practice.

Where the use of radioisotopes in medical institutions is to be limited to sealed radiation sources for well established intracavitary, interstitial or external therapeutic procedures, a medical isotopes committee is not necessary.

A. Teletherapy Unit

A separate announcement entitled, "Present Procedures of the Atomic Energy Commission for the Allocation of High Intensity Gamma Radioisotope Sources for Teletherapy Devices", is available from the Isotopes Extension upon request.

B. Sealed and Particulate Radiation Sources for Interstitial, Surface or Intracavitary Use

The physician should be (1) a qualified specialist in therapeutic radiology (diploma of the American Board of Radiology will serve as evidence of such qualification) in addition to having at least three years experience in therapeutic radiology or (2) a qualified specialist in another field (diploma of the respective specialty board will serve as evidence of such qualification) appropriate to the use being proposed, with training and experience in radiation dosimetry in addition to having at least three years experience in interstitial, surface or intracavitary use of radiation sources.

NOTE: If the radioisotope requested is to be used as an adjunct to or replacement for radium, information should be presented concerning the means by which radium dosages are to be converted to dosages in terms of the radioisotope requested and the procedure to be employed to account for the decay of the latter.

C. Beta-Ray Applicators

1. Superficial Lesions of the Eye

The physician should be a qualified specialist in therapeutic radiology, or ophthalmology (diploma of the appropriate specialty board will serve as evidence of such qualification), in addition to having at least three years experience in such specialty. The three years experience should include the use of beta-rays or soft x-rays in the treatment of superficial lesions of the eye. The applicant should furnish evidence of knowledge and experience concerning the problem associated with beta-ray depth dosage.

2. Superficial Lesions of the Skin

The physician should be a qualified specialist in dermatology or therapeutic radiology (diploma of the appropriate specialty board will serve as evidience of such qualification) in addition to having at least three years experience in such specialty. The three years experience should include the use of beta-rays or soft x-rays in the treatment of superficial lesions of the skin. The applicant should furnish evidence of knowledge and experience concerning the problems associated with beta-ray depth dosage.

NOTE: The present procedures of the Atomic Energy Commission for sealed radioisotope sources such as are contained in beta-ray applicators require that they be tested for leakage of radioactivity at intervals of 6 months. A separate announcement concerning leak testing requirements is available from the Isotopes Extension.

IX. RADIOACTIVE MATERIALS AND SERVICES

The radioactive materials and special irradiation services available from the Atomic Energy Commission are described in the catalogs and bulletins issued by the operating contractors of the Commission; the Oak Ridge National Laboratory, Brookhaven National Laboratory, Argonne National Laboratory and National Reactor Testing Station. A number of commercial concerns also offer materials and services in areas of radioisotope distribution.

NOTE: When purchasing radiomaterials or related services from an AEC distributor (e.g. Oak Ridge National Laboratory), all non-federal applicants must use a special "Radioisotope and Service Irradiation Order Form" (Form AEC-391) and federal agencies must use an "Isotope Order Blank" (Form AEC-375). The isotope order blank and isotope order form incorporate certain terms and conditions; copies are available from AEC distributors and the Isotopes Extension. These forms are not intended for use when ordering materials from other than AEC distributors.

STANDARD FORM NO. 64

Office Memorandum • UNITED STATES GOVERNMENT

NO. 3

TO : Chief, Professional Division
Chief, Medical Plans and Operations Division
Chief, Legal Office (IN TURN)

DATE:

FROM : Chief, Medical Statistics Division

SUBJECT: Forms for Authorization of Radiation Therapy

1. Reference is made to conversation between Colonel Lodmell and Mr. Allen, 29 November 1956.

2. For patients not on active military duty, this division agrees with the position expressed in Memo No. 2 above, that the patient's consent for a surgical procedure or other therapeutic procedure which carries an unusual risk should invariably be required in writing and witnessed. However, it is believed to be essential, in the interest of standard governmental medicolegal practice, that this consent be recorded on Standard Form 522, Authorization for Administration of Anesthesia and Performance of Operations and Other Procedures (copy attached), rather than on local forms such as those described in Inclosure No. 1.

3. It will be noted that Standard Form 522 provides for recording consent, but no specific provision is made for "a written statement from the patient... clearly expressing understanding of...the special treatment." (Regan, as quoted in Memo No. 2 above.) In the opinion of this division, such specific provision is unnecessary. The patient's written consent is believed to be a sufficient implication of his understanding, on the one hand; on the other, it appears doubtful that an explicit signed statement that the patient "understood" would be accepted as proof or even evidence that he did in fact understand.

4. It will be noted, also, that SF 522 does not include reference to any medical counselling given a patient who is consenting to a surgical or other procedure. It is believed, however, that medical records should include a statement that patients have been counselled as to the nature, expected results of, and risks involved in procedures for which written consent is required. This division will recommend changes to AR 40-424, Preparation and Maintenance of Clinical Records, which will require that physicians include such statements, when appropriate, as "progress notes" in the clinical record. If there is legal or medical opinion that the patient rather than the physician should sign such a statement of counselling, it appears that the statement should be made a part of SF 522. In that case, this division will initiate a request that the Interagency Committee on Medical Records consider whether revision of the form should be undertaken.

1 Incl
a/s

Eugene L. Hamilton
EUGENE L. HAMILTON
Chief, Medical
Statistics Division

Standard Form 522
(Transmitted May 1950
by Bureau of the Budget
Circular A-32 (Rev.)

CLINICAL RECORD

AUTHORIZATION FOR ADMINISTRATION OF ANESTHESIA AND PERFORMANCE OF OPERATIONS AND OTHER PROCEDURES

(The granting of this authorization does not constitute a waiver of an individual's rights under the provisions of title 28, United States Code with reference to Federal tort claims.)

NAME OF MEDICAL FACILITY _____ DATE _____

1. I hereby consent to the performance upon myself or name of patient _____

of _____
(State nature of operation or procedure, as: "an operation to remove appendix")

2. I further consent to the administration of such anesthesia as may be considered necessary or desirable in the judgment of the medical staff of the above-named medical facility.

3. I further consent to the performance of such additional operations or procedures as are considered necessary or desirable in the judgment of the medical staff of the above-named medical facility.

4. I also consent to the disposal by authorities of the above-named medical facility of any tissues or parts which it may be necessary to remove.

(Cross out any paragraphs above which are not appropriate.).

Signature of patient _____

When patient is unable to affix signature:

Signature of person authorized to consent for patient _____

WITNESS: Signature _____

Address _____

City and State _____

Date _____

PATIENT'S LAST NAME—FIRST NAME—MIDDLE NAME	REGISTER NO.	WARD NO.

(NAME OF HOSPITAL OR OTHER MEDICAL FACILITY)

AUTHORIZATION FOR ANESTHESIA, OPERATIONS, ETC.
Standard Form 522

U. S. GOVERNMENT PRINTING OFFICE 16—61862-1

my draft for MB's signature

MCHDK-E 12 March 1957

Vice Chancellor
Schools of the Health Professions
University of Pittsburgh
Pittsburgh 13, Pennsylvania

Dear Sir:

This is in reply to letter dated 18 February 1957, from Dr. Paul H. Maurer regarding work to be performed under Contract No. DA-49-007-MD-2[illegible].

In connection with your request for a statement concerning the assumption of responsibilities by the Army for liabilities of Contractor incurred in the performance of subject contract, your attention is invited to the provisions of ASPR-7-203.22, Insurance--Liability to Third Persons, copy attached, and particularly to the provisions of the first sentence of paragraph (c), which Article represents the maximum protection which can be afforded contractors under present policy. It is our intention to make this article available to you under this contract, contingent upon your adhering to the following principles, policies, and rules for the use of human volunteers in performing subject medical research contracts.

1. The voluntary consent of the human subject is essential. This means that the person concerned:

   a. Should have legal capacity to give consent.

   b. Should be so situated as to be able to exercise free power of choice, without intervention of force, fraud, deceit, duress, over-reaching, or other form of constraint or coercion.

   c. Should have sufficient knowledge and understanding of the experiment to enable him to make an enlightened decision, on the basis of explanation given to him as specified below.

   d. Should state his consent in writing, signed in the presence of at least one witness who shall attest to such signature in writing.

2. Each individual who initiates, directs or engages in the experiment has a personal duty and responsibility for ascertaining the quality of the volunteer's consent.

3. Before the acceptance of consent of the volunteer, he must be given adequate explanation. He should be informed of the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonably to be expected; and the effects upon his health or person which may possibly come from his participation in the experiment.

4. The experiment should be such as to yield fruitful results for the good of society, unprocurable by other means of study, and not random and unnecessary in nature.

5. The number of volunteers used must be kept at a minimum consistent with the requirement of a fruitful experiment for the good of society.

6. In order that the anticipated results will justify doing the experiment, it (the experiment) should be designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problem under study.

7. The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury.

8. No experiment should be conducted where there is a prior reason to believe that death or disabling injury will occur.

9. The degree of risk to the volunteer should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.

10. The experiment should be conducted only by scientifically qualified persons (including an adequately trained physician) who shall be required to exercise the highest degree of skill and care throughout the experiment. Competent consultants should be available on short notice in this connection.

11. Adequate preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability, or death. This includes hospitalization and medical treatment as may be required.

12. The human volunteer subject should be at liberty to bring the experiment to an end if he feels that it is impossible for him to continue under the test.

13. The scientist or physician in charge must be prepared to terminate the experiment at any stage, if he has probable cause to believe, in the exercise of the good faith, superior skill and careful judgment required of him that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject.

14. Established policy prohibits the use of prisoners of war in human experimentation. They will not be used under any circumstances.

15. Agents used in research must have the following limiting characteristics:

a. Controllable lethality

b. No serious chronicity anticipated

c. Effective therapy available

d. Adequate background of animal experimentation.

Sincerely yours.

cc: Dr. Maurer

MAX H. BROWN
Lt. Colonel, MSC
Contracting Officer

CONCURRANCE:

_____
Chief, Legal Office

_____
Chief, Research & Development
Division

MJ/csl

MEDDL-B

8 May 1957

Dr. Robert A. Moore
Vice Chancellor
Schools of Health Professions
University of Pittsburgh
Pittsburgh 13, Pennsylvania

RE: Contract No. DA-49-007-MD-248

Dear Dr. Moore:

Reply has not been received to our letter of 12 March 1957, regarding policies for the use of human volunteers in performing medical research contracts.

We are wondering if there is any additional information that might be required from this office regarding the subject presented. We had expected to receive a statement from you that the work would be conducted in accordance with the policies set forth in our letter of 12 March, prior to modifying the contract to include the "Liabilities to Third Persons Clause."

Sincerely yours,

MAL S. BROWN
Lt. Colonel, MSC
Contracting Officer

Penalties in Experiments

UNIVERSITY OF PITTSBURGH
PITTSBURGH 13, PENNSYLVANIA

OFFICE OF THE VICE CHANCELLOR
FOR THE HEALTH PROFESSIONS

May 16, 1957

RE: Contract No. DA-49-007-MD-248

Lt. Colonel Max H. Brown, MSC
Contracting Officer
Department of the Army
Office of the Surgeon General
Washington 25, D.C.

Dear Colonel Brown:

This is in answer to your inquiry of May 8 on the use of human volunteers in performing a medical research contract issued to the University with the principal investigator as Dr. Paul Maurer.

We have discussed this matter a number of times since receiving your letter and are in process of appointing an Advisory Committee within all schools of the University. I may say that everyone approves in principle of the statement which you sent. We believe it represents an excellent basis for proceeding in each individual instance. However, we are of the opinion that each such experiment should be passed on by an all University committee; if for nothing more than to give the investigator moral backing that what he proposes is sound.

Sincerely yours,

Robert A. Moore

Robert A. Moore
Vice Chancellor
Health Professions

UNIVERSITY OF PITTSBURGH
SCHOOL OF MEDICINE
PITTSBURGH 13, PENNSYLVANIA

DEPARTMENT OF PATHOLOGY

February 13, 1957

Major Charles C. Pixley
Chief, Surgical Research Branch
Research and Development Division
Department of the Army
Office of the Surgeon General
Washington 25, D. C.

Dear Major Pixley:

I am enclosing copies of the protocols of the next experiments involving medical students. The following materials are to be investigated for antigenicity in man:

a. SPPS Bi 21 which was received from Dr. Robert Pernell.

b. Heated liquid plasma lot 230C30 received from Hyland Laboratories.

The procedure will be as follows:

1. 50 ml. of blood will be drawn from the volunteers.

2. They will then be skin tested with the material.

3. The students will then receive a total of 5 1 ml. injections of the material (subcutaneously or intramuscularly) over a period of 10 days.

4. Both ten days and about three weeks after the last injection 50 ml. of blood will be drawn from the volunteers and, they will be skin tested as mentioned above.

All of the above procedures will be performed with sterile techniques.

Although the students have volunteered for these experiments I would appreciate receiving a formal approval for this work from the Department of the Army. As mentioned in our discussions, a statement concerning the assuming of responsibility by the Army for any possible untoward effects resulting from this experimentation should accompany the approval.

I deeply appreciate your understanding in this matter.

Sincerely yours,

Paul H. Maurer, Ph.D.

PHM:sas

JK

AFEB copy return

Minutes, Spring Meeting, AFEB
2-4 May 1957. Conference Room 341
WRAIR, WRAMC

Present were: Board Members (2-3-4 May)	Dr. Dingle, Presiding			
	Drs. Francis	Kern	MacLeod	
	Drs. Shepard	Shope	Smith	
	Dr. Wood (2 and 4 May only)			
Absent:	Dr. Stebbins, who expressed regret at not being able to attend.			
Commission Directors: (2-3 May)	Drs. Beard	Cheever	Davenport	
(2-3 May)	Drs. Feller	Hammon	McFarland (2 May only)	
(2-3-4 May)	Drs. Shope	Smadel (3 May only)	Weller (2-3 May)	
(2-3 May)	Dr. Wilson			
Absent:	Dr. Pillsbury			
	Dr. Edsall (represented by Dr. Gauld)			
Representatives, D/A: (3 May)	Major Gen. S.B. Hays, The Surgeon General			
(3 May)	Col. J.H. Gordon, MC, Prev Med Div, OTSG			
(2 May)	Col. R.L. Callison, MC, Prev Med Div, OTSG			
(2-3-4 May)	Col. R.L. Hullinghorst, MC, Res & Dev Div, OTSG			
(2-3 May)	Col. A.F. Long, U.S. Army Hq. 6			
(2-3-4 May)	Col. R.P. Mason, WRAIR			
(4 May)	Col. W.D. Tigertt, MC, WRAIR			
(2-3 May)	Col. P.R. Beckjord, MC, WRAIR			
(2-3 May)	Lt. Col. A.S. Benenson, MC, WRAIR			
(2 May)	Lt. Col. F.W. Timmerman, MC, Res & Dev Div, OTSG			
(2 May)	Lt. Col. D. Crozier, MC, Prof Div, OTSG			
(2-3-4 May)	Lt. Col. H.L. Ley, Jr., MC, Res & Dev Div, OTSG			
(2-3 May)	Lt. Col. R.D. Barron, MC, RCAMC			
(2-3 May)	Major A.M. Reeve, MC, Prev Med Div, OTSG			
Representatives, D/N: (2-3 May)	Capt. H.K. Sessions, MC, Prev Med Div, BuMed			
(2-3 May)	Capt. J.R. Kingston, MC, Res Div, BuMed			
(2 May)	Capt. S.A. Britten, MC, Prev Med Div, BuMed			
(2 May)	Capt. J.R. Seal, MC, Prev Med Div, BuMed			
Representatives, D/AF: (2-3 May)	Lt. Col. G.F. Fisher, MC, Prev Med Div, USAF			
Others: (2-3 May)	Dr. S. Bayne-Jones, USAR, Retired			
(2-3-4 May)	Dr. Floyd W. Denny, Ass't to President, AFEB			
(2-3 May)	Dr. Herman N. Eisen, Washington University			
(2-3 May)	Dr. Ross L. Gauld, WRAIR			
(3 May)	Dr. Harold B. Houser, State University of N.Y.			
(2-3 May)	Dr. William S. Jordan, Western Reserve Univ.			
(2 May)	Dr. Howard T. Karsner, BuMed, D/N			
(2 May)	Dr. Barry G. King, CAA			
(2-3 May)	Dr. Charles H. Rammelkamp, Jr., Cleveland City Hos.			
(2 May)	Dr. C.A. Smith, CDC, Public Health Service			
2-3 May)	Dr. John C. Snyder, Harvard School of Pub. Hlth.			
(3 May)	Dr. Arthur Stull, OTSG/DA			
Staff: (2-3-4 May)	Capt. R.W. Babione, MC, USN, Executive Secretary			
AFEB (2-3 May)	Lt. Col. R.E. Dockery, USAF(MC), Asst. Ex. Sec'y.			

reconsider the efficacy of gas gangrene antitoxin. Dr. Dingle stated that in December of 1955 the Board had recommended that dried anti-toxin be made available and, if there was still some question concerning this action, that the matter should be referred back to the Commission on Immunization. He then requested that Colonel Hullinghorst write a letter re-opening this matter.

2) ROTATION OF COMMISSION DIRECTORS

Dr. Dingle stated that in 1954, the Board had recommended that Commission Directors serve a maximum of two terms of two years each. Since that time, some doubt had arisen as to the desirability of this action, particularly with reference to new Commissions. The desirability of maintaining continuity favored reverting to the old policy of an unrestricted number of terms. It was pointed out that since there is rotation among military personnel, similar rotation of Commission Directors may not be desirable. Opinions were expressed on both sides but the consensus was that the present policy was not satisfactory. A motion was made to rescind the action of the Board limiting the term of a Director to four years. This motion was seconded and passed unanimously.

3) NEWS RELEASES

Dr. Dingle requested that, when scientific data are released to the press, every effort be made to give credit to the Army, the AFEB, and the Research & Development Division for their support, and also that the Research and Development Division be notified of all press releases. A directive concerning news releases, publication of data, and related matters, is being written and will be distributed shortly by the Research & Development Division.

4) COPIES OF CORRESPONDENCE

Dr. Dingle reminded the Commission Directors that copies of all correspondence concerning Commission activities should be sent to Captain Babione, the Executive Secretary, Colonel Ley of the Research & Development Division, and to the office of the President. He emphasized the necessity of Commission Members sending carbon copies of their correspondence to the Director of their respective Commissions.

5) BUDGETS

Dr. Dingle emphasized the necessity of long range planning (5-10 years), with respect to research programs and budgets, by both Board Members and Commission Directors, and suggested the possibility of Colonel Ley indoctrinating new Commission Directors in budgetary matters.

6) VOLUNTEER STUDIES AT WILLOWBROOK SCHOOL

Dr. Dingle re-opened the discussion on volunteer studies with hepatitis at Willowbrook School. The objections to this study were that viruses other than infectious hepatitis virus might be present in the tissue cultures used, that all other methods of demonstrating the presence of a virus had not been tried, and that the subjects involved in these studies were not

volunteers. Opinions were also expressed in favor of the study as outlined Dr. Dingle pointed out that legally the children are volunteers because they are guardians of the State, and permission had been obtained from State authorities. A motion was [illegible] protocol. In the final vote there were 17 votes for and 1 against this motion.

Dr. Davenport then made the following motion: "That it be required that all protocols for human experiments be in the hands of Commission Directors and Board Members at least thirty days before action is to be taken". This motion was seconded and passed unanimously.

7) AFEB AND CIVIL DEFENSE

Dr. Francis raised for discussion the possible connection between the AFEB and Civil Defense. Dr. Bayne-Jones stated that the mechanism of civilian defense was not definite at the present time, and that officially the armed services were not held accountable for civilian defense, but would probably have to assume responsibility in a time of emergency. Colonel Hullinghorst added that the laws concerning this problem were difficult to interpret, but that he believed that the personnel of the armed services were becoming more aware of their responsibility in the care and health of everyone, both military and civilian.

Chief, Research and Development Div., OTSG 5 August 1957

Contracting Officer, OTSG

The Use of Human Test Subjects in Medical Research supported by the Office of The Surgeon General

1. Inclosure No 1, is a copy of Memo drafted by the contracting officer primarily for discussion purposes of subject problem. It reflects generally the current thinking of the contracting officer.

2. Inclosure No 2, is a copy of a paper received from the Legal Office on the same subject.

3. It is requested that the R&D Division comment on subject problems in order that steps can be taken to initiate necessary procedures to handle this delicate subject.

Contracting Officer

2 Incls
a/s

MAX H. BROWN
Lt. Colonel, MSC

3 April 1957

SUBJECT: The Use of Human Test Subjects in Medical Research Supported by the Office of The Surgeon General

1. It is believed to be appropriate to segregate this subject into the following categories:

a. Research that is conducted by an institution with monetary support from OTSG. The institution, because of its primary interest, would conduct the research program even without support of the OTSG.

b. Research that is supported by the OTSG because of its primary interest. In other words the study is conducted at the insistence of the OTSG.

2. In cases where human subjects are used in research falling in category a, consideration should be given to the utilization of Cost-Sharing Contracts, to the extent that the institution would bear all the costs of insurance, liabilities to third parties, etc., and assume all responsibility for any possible effects resulting from the experimentation.

3. In those cases where human subjects are used in research falling in category b, the OTSG to assume its full responsibility and provide by contractual arrangement through the use of the article shown in ASPR 7-103.22, Insurance - Liability to Third Persons. Further, by contractual arrangement either by reference or by inclusion in the contract, incorporate [redacted], the contents of RDD Publication dated

12 March 1954, subject: "Use of Human Volunteers in Medical Research;" Principle, Policies and Rules of the Office of the Surgeon General.

4. In addition, the Project Officer of the Research and Development Division should furnish the Contracting Officer a firm recommendation on this subject for each case involved. Further, official files should be fully documented on all cases where research supported by the OTSG involves the use of Human Test Subjects.

7 2

Volunteers for Medical Experiments

SUBJECT: Contracts for Medical Research Where it is Planned to Use Human Subjects

1. It is believed to be administratively desirable in order to fully protect The Surgeon General in subject instances that the following Procedure be strictly adherred to:

a. Incorporate into subject Contracts Article shown in ASPR 7-103.22, Insurance Liability to Third Persons.

b. Incorporate into the Contract by reference or by inclusion, the Principals, Policies and Rules of the Office of The Surgeon General on the use of Human Test Subjects.

c. The Research and Development Project Officers acquaint the Contracting Officer by memorandum on each proposed contract when it is known that Human Test Subjects will be used.

d. Project Officers to include in the memorandum a record of any correspondence or verbal discussion held with the Principal Investigator or other Technical or Administrative Personnel.

Codes 3

II

HEADQUARTERS
AIR RESEARCH AND DEVELOPMENT COMMAND
U. S. AIR FORCE
Andrews Air Force Base
Washington 25, D. C.

RDTHA 12 September 1958

SUBJECT: Conduct of Hazardous Human Experiments

TO: RADC APGC AFSWC AFMDC AFBMD (ARDC)
WADC AFCRC AFMTC AFFTC AFOSR

1. This letter tells when humans may be used in conducting hazardous research and development tests. It explains procedures and factors to be considered before approving tests.

2. Policy. The effective conduct of research and development effort will, upon occasion, require the use of humans for inherently hazardous experiments. It will be the policy of ARDC that the approving authority will evaluate the need for test results and insure that the test subject(s) are afforded every known reasonable safety precaution during the conduct of the test. No test will be conducted without the prior knowledge of Headquarters ARDC.

3. Responsibilities:

a. The ARDC center or detachment commander responsible for the research and development project being supported by the test is delegated authority to approve the hazardous human experiment or test. This responsibility will not be redelegated.

b. The commander approving the experiment or test will notify the Deputy Commander for Research and Development, Headquarters ARDC, at least 5 working days prior to commencement of tests.

4. General. This letter is applicable to tests, the conduct of which may result in injury to the subject and which, once commenced, cannot be controlled or terminated by individuals conducting the test or the test subject. Such tests are usually assigned to determine a level of human tolerance for a condition which may be imposed because of Air Force operations or to determine the adequacy of equipment designed for human use. Typical examples are live ejection tests, balloon-borne environmental studies, track tests, and high altitude bailout studies. This letter does not apply to flight tests, tests of a purely clinical medical nature and routine parachute and personal equipment development tests.

5. Use of Evaluation Guide for Testing Requirements and Possible Hazards to Participants. To insure that an orderly, comprehensive process of review occurs prior to the exposure of individuals to risks involved

in human experimentation, the responsible commander will approve the use of human beings in experiments or tests only after he has evaluated information gathered from the Evaluation Guide for Testing Requirements and Possible Hazards to Participating Personnel in the Conduct of Hazardous Human Experiments (see attachment 1).

6. Exception to Administrative Procedures Required by ARDCM 80-4. The conduct of hazardous human experiments is exempt from the provisions of chapter 3, section IV, subsection I, ARDCM 80-4, that requires the submission of ARDC Form 105, "R&D Test Annex," for research and development tests.

7. Requirements for Headquarters ARDC Notification. The approving commander will notify the Deputy Commander for Research and Development, Headquarters ARDC at least five working days prior to the start of tests. This notification may be made by electrical message, letter, or official briefing. Reference will be made to this letter and the following information will be provided:

a. Project number.

b. Purpose of tests and justification for human risk.

c. Description of planned test procedures.

d. Expected number of tests.

e. Expected period of tests.

f. Test site.

8. When Reconfirmation of Test Approval and Renotification of Headquarters, ARDC is Required. Radical changes in techniques and equipment resulting from initial test experience and prolonged delays in testing will require the responsible commander to:

a. Re-evaluate the test program.

b. Reapprove the test program.

c. Renotify the Deputy Commander for Research and Development, Headquarters ARDC.

9. Disposition of Records:

a. A copy of the documentation which authorizes the conduct of hazardous human experiments will be filed in the applicable project file folder and retired (Authority: paragraph 61b, AFM 181-5).

b. All other copies will be destroyed after 90 days or upon completion of test, whichever is sooner (Authority: paragraph 58, AFM 181-5).

10. Reports Control. The reporting requirements contained herein are exempt from assignment of a reports control symbol in accordance with the provisions of paragraph 7b(11), AFR 174-1.

/s/ L. I. Davis
L. I. DAVIS
Major General, USAF
Deputy Commander/Research & Development

1 Incl
Evaluation Guide

EVALUATION GUIDE FOR TESTING REQUIREMENTS AND POSSIBLE HAZARDS TO PARTICIPANTS IN THE CONDUCT OF HAZARDOUS HUMAN EXPERIMENTS

1. All necessary preliminary exploratory laboratory, dummy and animal tests have been conducted and evaluated? Human subject testing is the only remaining means of providing the final validation?

2. The need for the test results justifies the degree of probable risk to the test human being?

3. Test procedures have been planned in a manner which reduces potential hazard factors to the lowest practical level?

4. The fabrication techniques, quality of material, and quality of workmanship of equipment to be used have been approved by qualified responsible people?

5. The subject is a volunteer and understands the degree of risk involved in the experiment?

6. Subject(s) to undergo tests have been adequately selected and trained.

7. Qualified physicians will be on the scene during the conduct of the test or tests?

8. Decisions during the day-to-day test operations pertaining to the adequacy of weather, support provisions, health and mental well-being of the subject(s) will be made by qualified individuals conducting the test effort--not the individual(s) undergoing the test or experiment?

9. Tests will receive necessary support in the form of aircraft, photography, instrumentation, etc., in order that the tests may be completed with a minimum of exposures?

10. Qualified individuals from other ARDC organizations, other major commands, other government agencies, educational institutions, and/or private industry have been consulted regarding any of the above-listed factors that cannot be adequately evaluated by persons under the jurisdiction of the approving authority?

Incl 1

GENERAL COUNSEL'S OPINION, VETERANS ADMINISTRATION - OP. G. C. 28-58

Chief Medical Director 4-8

General Counsel June 25, 1958

Legal aspects of medical research

1. This has reference to your recent memoranda raising a number of legal questions with respect to two proposed research projects. One memorandum, on the subject of "Research Project entitled 'Tubeless Measurement of Gastrointestinal Motility' (#M31-256)", concerns The R Institute for Medical Research in connection with the VA Hospital, Manhattan, New York. The other memorandum, on the subject "Research Grant Funds", concerns The W Laboratories of Chicago and the VA Hospital, Chicago, with respect to a study of the "Physiology of Intrinsic Factor", as further defined in the memorandum.

2. The file contains the following data relating to the proposed project in New York City:

"Preliminary discussions have been carried out with Dr. _____ of Corporation _____ and The R Institute, on the subject of the possibility of making a pressure-sensitive device which would record intraluminal pressures without an attached tube. This capsule-shaped device would be approximately 1 cm. in diameter and 1.5 cm. in length, coated with plastic. The device is swallowed by the patient and subsequently passes through the gastrointestinal tract. During its course through the stomach, small intestine and colon intraluminal pressures are detected by microphones in the wall of the capsule. This signal is transmitted to an external receiver and recorder by means of an amplifier and oscillator, powered by a tiny battery. Such subminiaturization is accomplished through the use of the transitor principle.

"Dr. _____ has stated that the construction of such a device is entirely possible, and has further stated that The R Institute and _____ Corporation _____ will undertake to build and test a prototype.

"It is proposed that, if laboratory and animal tests are satisfactory, this device be used to study motility of patients at this hospital."

3. The capsules have now been developed by The R Institute for Medical Research. In letter of October 30, 1957, its President writes to the VA as follows:

"We propose to lend to you upon the terms stated in this letter five devices known as 'radio pills,' which are designed to transmit a radio signal while within the human body, for the purpose of measuring digestive system functions. The devices to be loaned are more fully identified in the attached schedule. The terms of this loan are as follows:

"1. We will receive no consideration from you for the loan of the devices, and reserve the right at any time to request you to return them, and upon such request you will return them promptly and in good condition subject to ordinary wear and tear.

"2. The devices will at all times be in your possession and it is understood that they will be used only for experimental purposes and under the supervision of qualified Veterans Administration personnel. These devices have not yet been fully tested human subjects, but we have concluded that the following procedures should be observed in the course of any experimentation involving a human subject who has taken the device internally, for the protection of the subject and the success of the experiment:

"a. Care should be taken to be sure that the intestinal tract of the humal subject is sufficiently unobstructed to permit clear passage of the device.

"2. The inhibition of endogenously secreted Intrinsic Factor in non-pernicious anemia patients, as a result of the exogenous porcine Intrinsic Factor.

"3. Anatogism of non-pernicious anemia patients to heterologous Intrinsic Factor Concentrate

"The proposed study will test these hypotheses in a series of normal volunteers and patients with various diseases.

"The effect of porcine Intrinsic Factor Concentrate will be quantitatively compared with that of human gastric juice using pernicious anemia patients and the Co58 labelled cyanocobalamin technique. The W Laboratories will supply a number of chemically fractionated Intrinsic Factor Concentrate preparations to be tested for their Intrinsic Factor potency and also for their inhibitory effects. This will be designed to investigate the first hypothesis described above.

"It is contemplated that this study will involve approximately 20 or more normal volunteers and 20 or more pernicious anemia patients.

"If you are agreeable to carrying out this work, and it acceptable to the Veterans Administration West Side Hospital, we will issue a check to the Veterans Administration West Side Hospital for $1250.00, representing the first quarterly payment. The balance will be paid quarterly during 1958.

"In addition, we will include a check for $500.00 to be used as a fund for paying volunteers necessitated by this study. It is understood that where payment is necessary, the volunteer will receive either $10.00 or $20.00, depending upon the type of experiment. Disposal as of December 1958 of any unexpended or unallocated portion of the fund of $500.00 will rest with The W Laboratories.

"You will inform us from time to time and at the conclusion of the study as to results obtained.

"We are enclosing herewith three signed copies of this agreement. If it is acceptable to you and the Hospital, will you kindly sign one and return it to us? You may retain the other two for your own files and that of the Hospital."

The correspondence shows that volunteers would take weekly doses of Co58 Cyanocobalamin, 0.5 microcuries per dose, for three consecutive weeks. They will be paid from funds provided by The W Laboratories: Twenty or more volunteers will be selected from pernicious anemia patients in the VA hospital. The other twenty volunteers will be university students who, in connection with their studies, would devote part of their time to various duties at the hospital.

1. The basic question presented is whether the VA may enter into the research proposed in each case, and if so, under what conditions. It is further asked whether the VA will be responsible for any adverse effects upon the volunteers.

2. The VA has authority to undertake research and enter into contracts for research purposes, wherein the objective is the health and welfare of veteran-patients or domiciliaries. The current appropriation act, Public Law 85-69 provides that $10,344,000 shall be available for medical research. Section 1716, Public Law 85-56, 38 USC 1716, continues the authority formerly contained in section 1500 of Public Law 346, 78th Congress, as amended, 38 USC 697, granting the Administrator the power to enter into contracts for research purposes. --86 Sol 349; 90 Sol 624, 627. Section 215, Public Law 85-56, 38 USC 2215, expressly provides for research in certain limited fields.

a. By express agreement. Such agreements are upheld, in general, except where one party is at an obvious disadvantage in bargaining power.

b. By implication from the conduct of the parties. When the plaintiff enters voluntarily into a relation or situation involving obvious danger, he may be taken to assume the risk, and to relieve the defendant of responsibility. Such implied assumption of risk requires knowledge and appreciation of the risk, and a voluntary choice to encounter it."

A similar conclusion is set forth in the "Restatement of the Law" of the American Law Institute on the subject "Torts", sections 49, 892, and 893; 86 Corpus Juris Secundum on "Torts", section 12; and 52 American Jurisprudence on "Torts", section 94.

13. In line with the foregoing, if the research is to be undertaken, it would be necessary that the VA obtain from each volunteer a written consent, whether the volunteer will be paid or not. The volunteers must be competent to give consent. A form should be prepared for signature by each one, setting forth the objects of the research and the risk involved, and containing further a statement substantially as follows:

"I understand that this research is for experimental purposes, and results cannot be fully foreseen. Preliminary tests have been made, and indicated precautions to protect volunteeers have been taken. The VA does not represent that any injury will necessarily be avoided in every instance even when these precautions are followed. Nevertheless, I voluntarily assume the risk involved, in order to advance medical knowledge. I will carefully follow instructions given by the VA for the conduct of the experiment. I will not make any claim or demand upon the VA or its personnel for injury, if any arises from the experiment. This does not relieve the VA of negligence in the performance of the experiment.

"I understand that I am to observe the following instructions (or the instructions attached hereto), subject to such further instructions as the VA may give: . . . ."

14. It would be appropriate that there then follow a paragraph relating to release of information, which could read as follows:

"I agree that data obtained by the VA from this experiment may be used for medical or other scientific purposes, including publication, but my identity will not be revealed unless I expressly consent thereto."

15. The agreement drafted by The R Institute contains the following language in paragraph 3 thereof:

". . . The R Institute for Medical Research assumes no liability or responsibility of any kind to the Veterans Administration or to any human subject who may be used in the course of experimentation. . . .".

The foregoing is on the premise that the VA and not The R Institute is conducting the research. This premise is correct. However, it does not relieve The R Institute of negligence in the preparation of the "radio pills".

16. In summary, the VA may conduct the research projects proposed in conjunction with The R Institute for Medical Research and with The W Laboratories, respectively, subject to the foregoing.

GUY H. BIRDSALL

Distribution:

C.A.'s, R.O. & Centers with R.O. activities	2
Veterans Benefits Office	111
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Managers - all Field Stations, Attn: Medical	2
Manager all Field Stations	2

5 --

University of Pittsburgh
Pittsburgh 13, Pa.

November 20, 1953

Dr. John F. Enders
Chief, Research Division of Infectious Diseases
Children's Medical Center
300 Longwood Avenue
Boston 15, Massachusetts

Dear John:

This is to confirm our telephone call of this morning, November 20th, regarding approval of the AFEB for the protocol of the experiment which you propose to carry out with Dr. Henry Kempe at Denver with the attenuated measles strain in normal children.

I phoned Tommy Francis yesterday afternoon and he urges that this investigation and other similar subsequent ones, possibly with Robbins, Kurnen, or Woodward, be done in conjunction with you as a member of the Virus Infections Commission of the AFEB. Thus, each experiment using human volunteers will require that the protocol be approved by the Board.

Ordinarily the AFEB desires reasonable amount of time to consider these protocols in advance of a meeting. They will be meeting in Washington on December 8th and I will be present. Dr. Francis believes that since this protocol will be so similar to the previous one you submitted that, if this is distributed to members before the meeting, there will be no difficulty in getting consideration. I suggest that you send an adequate number of mimeographed copies to Captain Sabione as soon as possible for distribution to the Board members and a copy to me.

I am sending you a copy of a mimeographed statement dated 12 March 1954 entitled, "USE OF HUMAN VOLUNTEERS IN MEDICAL RESEARCH: PRINCIPLES, POLICIES AND RULES OF THE OFFICE OF THE SURGEON GENERAL" which were adopted by the Board as their general principles. You should take this into consideration in writing out the protocol and

Dr. John F. Enders

November 20, 1958

its attached statement. I think the important things to point out are the reasons for this experiment being considered necessary, i.e., normal children may possibly have less reaction than the mental defectives and be a means of determining whether the virus needs to be attenuated further. You will, of course, state the results of the last experiment, indicating why this one needs to be done. It is also important to indicate the source of the volunteers, the person who will be in charge of their follow-up, and who will be responsible for any medical care which might be needed.

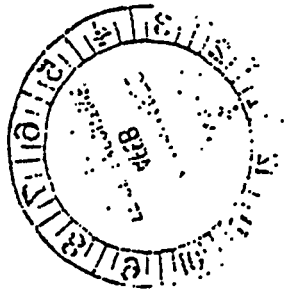
For subsequent experiments it would probably be wise to get the protocols worked out as far in advance as possible and the details of the arrangements to be made and the persons responsible, etc., and get applications for approval for this submitted to the Board just as soon as possible. It is hoped that if this is not near the time of a Board meeting, Dr. Francis can handle this by mail so delays on this important project will not be necessary.

Very sincerely yours,

W. McD. Hammon, M. D.
Director
Commission on Viral Infections

WMH/co
Enclosure

cc: Captain Babion
Dr. Francis



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ARMY REGULATION
No. 70-25

HEADQUARTERS,
DEPARTMENT OF THE ARMY
WASHINGTON, DC, 31 July 1974

RESEARCH AND DEVELOPMENT

USE OF VOLUNTEERS AS SUBJECTS OF RESEARCH

Effective 15 September 1974

This revision transfers the final approval authority from the Chief of Research and Development to The Surgeon General for all research using volunteers, except research involving nuclear and chemical warfare agents and identifies the requirement for use of active duty military personnel as volunteers and instructs major commanders to provide assistance in their recruitment. Local limited supplementation of this regulation is permitted, but is not required. If supplements are issued, Army Staff agencies and major Army commands will furnish one copy of each to HQDA (DASG-RDZ), Washington, DC 20310. Other commands will furnish one copy each to the next higher headquarters.

1. Purpose. These regulations prescribe policies and procedures governing the use of volunteers as subjects in Department of the Army research wherein human beings are deliberately exposed to unusual or potentially hazardous conditions. These regulations are applicable worldwide, wherever volunteers are used as subjects in Department of the Army research.

2. Definition. For the purpose of these regulations, unusual and potentially hazardous conditions are those which may be reasonably expected to involve the risk, beyond the normal call of duty, of privation, discomfort, distress, pain, damage to health, bodily harm, physical injury, or death.

3. Exemptions. The following categories of activities and investigative programs are exempt from the provisions of these regulations:

a. Research and nonresearch programs, tasks, and tests which may involve inherent occupational hazards to health or exposure of personnel to potentially hazardous situations encountered as part of training or other normal duties, e.g., flight training, jump training, marksmanship training, ranger training, fire drills, gas drills, and handling of explosives.

b. That portion of human factors research which involves normal training or other military duties as part of an experiment, wherein disclosure of experimental conditions to participating personnel would reveal the artificial nature of such conditions and defeat the purpose of the investigation.

c. Ethical medical and clinical investigations involving the basic disease process or new treatment procedures conducted by the Army Medical Service for the benefit of patients.

4. Basic principles. Certain basic principles must be observed to satisfy moral, ethical, and legal concepts. These are—

a. Voluntary consent is absolutely essential.

(1) The volunteer will have legal capacity to give consent, and must give consent freely without being subjected to any force or duress. He must have sufficient understanding of the implications of his participation to enable him to make an informed decision, so far as such knowledge does not compromise the experiment. He will be told as much of the nature, duration, and purpose of the experiment, the method and means by which it is to be conducted, and the inconveniences and hazards to be expected, as will not invalidate the results. He will be fully informed of the effects upon his health or person which may possibly come from his participation in the experiment.

(2) The consent of the volunteer will be in writing. A document setting forth substantially the above requirements will be signed by the volunteer in the presence of at least one witness

*This regulation supersedes AR 70-25, 26 March 1962.

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Incl 12 to TAB B

not involved in the research study who will attest to such signature in writing.

(3) The responsibility for ascertaining the quality of the consent rests upon each person who initiates, directs, or conducts the experiment. It is a personal responsibility which may not be delegated.

b. The number of volunteers used will be kept at a minimum consistent with *c* below.

c. The experiment must be such as to contribute significantly to approved research and have reasonable prospects of yielding militarily important results essential to an Army research program which are not obtainable by other methods or means of study.

d. The experiment will be conducted so as to avoid all unnecessary physical and mental suffering and injury.

e. No experiment will be conducted if there is any reason inherent to the nature of the experiment to believe that death or disabling injury will occur.

f. The degree of risk to be taken will never exceed that determined to be required by the urgency or importance of the Army program for which the experiment is necessary.

g. Proper preparations will be made and adequate facilities provided to protect the volunteer against all foreseeable possibilities of injury, disability, or death.

h. The experiment will be conducted only by scientifically qualified persons. The highest degree of skill and care will be required during all stages of the experiment of persons who conduct or engage in the experiment.

i. The volunteer will be informed that at any time during the course of the experiment he will have the right to revoke his consent and withdraw from the experiment, without prejudice to himself.

j. Volunteers will have no physical or mental diseases which will make the proposed experiment more hazardous for them than for normal healthy persons. This determination will be made by the project leader with, if necessary, competent medical advice.

k. The scientist in charge will be prepared to terminate the experiment at any stage if he has probable cause to believe, in the exercise of the good faith, superior skill, and careful judgment required of him, that continuation is likely to result in injury, disability, or death to the volunteer.

l. Prisoners of war will not be used under any circumstances.

5. Additional safeguards. As added protection for volunteers, the following safeguards will be provided:

a. A physician approved by The Surgeon General will be responsible for the medical care of volunteers. The physician may or may not be the project leader but will have authority to terminate the experiment at any time that he believes death, injury, or bodily harm is likely to result.

b. All apparatus and instruments necessary to deal with likely emergency situations will be available.

c. Required medical treatment and hospitalization will be provided for all casualties.

d. The physician in charge will have consultants available to him on short notice throughout the experiment who are competent to advise or assist with complications which can be anticipated.

6. Approval to conduct experiment. It is the responsibility of the head of each major command and other agency to submit to The Surgeon General a written proposal for studies which come within the purview of this directive. The proposal will include for each study the name of the person to be in charge, name of the proposed attending physician, and the detailed plan of the experiment. The Surgeon General has final approval authority for all research using volunteers except research with nuclear or chemical warfare agents. Proposals for research with nuclear or chemical warfare agents will be forwarded to The Surgeon General with recommendations on medical aspects to the Secretary of the Army for approval.

7. Civilian employees. When civilian employees of the Department of the Army volunteer under this program, the following instructions will be observed:

a. Any duty as a volunteer performed during the employee's regularly scheduled tour of duty will be considered as constructive duty for which straight time rates are payable. Time spent in connection with an experiment outside the employee's regularly scheduled tour will be considered as voluntary overtime for which no payment may be made nor compensatory time granted. The employee will be so informed before acceptance of his volunteer services.

b. Claims submitted to the Bureau of Employees' Compensation, U.S. Department of Labor, because of disability or death resulting from an employee's voluntary participation in experiments, will include a citation to title 10,

PARA 8b

United States Code, section 4503 as the Department of the Army authority for the use of such volunteer services.

c. All questions concerning hours of duty, pay, leave, compensation claims, or application of other civilian personnel regulations to volunteer employees will be presented through channels to the Deputy Chief of Staff for Personnel, ATTN: Office of Civilian Personnel.

8. **Recruitment of active duty military volunteers.** Some research will require active duty military personnel as volunteers because of the nature of the investigations. Recruiting is best accomplished by research personnel responsible for conduct of the research. Major commanders will provide assistance to recruiting teams. At all times recruiting will be conducted in a morally, ethically, and legally acceptable manner.

APPENDIX

LEGAL IMPLICATIONS

The following opinions of The Judge Advocate General furnish specific guidance for all participants in research using volunteers:

1. Authority. The Secretary of the Army is authorized to conduct research and development programs including the procurement of services that are needed for these programs (10 U.S.C. 4503). The Secretary has the authority to "assign detail and prescribe the duties" of both members of the Army and civilian personnel (10 U.S.C. 3012(e)).

2. Military personnel and Department of the Army civilian employees. Compensation for the disability of death of a civilian employee resulting from personal injury or disease proximately caused by his employment is payable under the Federal Employees Compensation Act (39 Stat. 742 et seq.), as amended (5 U.S.C. 751 et seq.), regardless of whether his employment was of a hazardous nature. The amount and type of disability compensation or other benefits payable by reason of the death or disability of a member of the Army resulting from injury or disease incident to service depends upon the individual status of each member, and is covered by various provisions of law. It may be stated generally that under present laws no additional rights against the Government will result from the death or disability of military and civilian personnel participating in experiments by reason of the hazardous nature of the operations.

3. Private citizens. It is the policy of the United States to prohibit the acceptance of voluntary services particularly when they may provide a basis for a future claim against the Government. (R.S. 3679, as amended; 31 U.S.C. 665(b)).

4. Use of appropriated funds for the purchase of insurance. As the payment of insurance premiums on the life of an officer or employee of the United States is a form of compensation which is not currently authorized; payment of those premiums is prohibited (R.S. 1765; *Commissioner of Internal Revenue* v. *Bonwit*, 87 F 2d 764 (2d Cir. 1937); *Canaday* v. *Guitteau*, 86 F 2d 303 (6th Cir. 1936); 24 Comp Gen. 648 (1945)).

5. Contractor's employees. There appears to be no legal objection to the use of employees of contractors in research and development experiments. It is the responsibility of the contracting officer to determine whether the terms of the contract are sufficiently broad to permit the participation of these employees. Generally, benefits to which private employees may become entitled by reason of death or disability resulting from their employment are payable under State law except persons covered by the survivors insurance provisions of the Social Security Act (49 Stat. 623, as amended (42 U.S.C. 402)). Reimbursement of the employer for additional costs by reason of this liability of his employees will depend upon the terms of each contract. These employees are not disqualified from prosecuting claims against the Government under the Federal Torts Claims Act (28 U.S.C. 2671 et seq., see AR 25-70). In cost reimbursement type research contracts with commercial organizations the cost of maintaining group accident and life insurance may be reimbursed to the contractor (subject to certain exceptions) under ASPR 15-205.16 provided that the approval of the head of the Procuring Activity is obtained (APP 10-551).

6. Irregular or fee-basis employees. Intermittent services of such employees are authorized. (For experts and consultants see Sec. 15, Act of 2 Au 1946 (60 Stat. 810; 5 U.S.C. 55a); Sec. 501, Do Appropriation Act, 1961 (74 Stat. 349); note AP. 30-204.1, CPR A7; Sec. 710 Defense Production Act of 1960 (64 Stat. 819; 50 U.S.C. App 2160); and for architects, engineers, and other technical and professional personnel on a fee basis, see 10 U.S.C. 4540.). Whether these employees can be detailed or assigned to the proposed experiments will depend upon the statutory authority for employment and the provisions of their employment agreement in each case. The Federal Employees Compensation Act, *supra*, in all probability applies with respect to these irregular and fee-basis employees for any injury or disease resulting from their employment, although a final determination in such cases will have to be made by the Bureau of Employees Compensation, Department of Labor. Subject to such restrictions and limitations as may appear in the statutory authority under which he is employed, it would appear that the Government may legally bear the expense of premiums upon the life of an irregular or fee-basis employee whose rate of compensation is not fixed by law or regulations. In this regard, it may be advisable for the Government to provide ar

additional allowance to the employee for financing such private insurance arrangements as he may wish to make rather than to undertake direct negotiations with insurance carriers for the desired coverage.

7. Conclusion. Subject to the above conditions, Armed Forces personnel and/or civilians on duty at installations engaged in research in subject fields will be permitted to actively participate in all phases of the program.

The proponent agency of this regulation is the Office of The Surgeon General. Users are invited to send comments and suggested improvements on DA Form 2028 (Recommended Changes to Publications and Blank Forms) to HQDA (DASG-RDZ), WASH DC 20310.

By Order of the Secretary of the Army:

CREIGHTON W. ABRAMS
General, United States Army
Chief of Staff

Official:
VERNE L. BOWERS
Major General, United States Army
The Adjutant General

DISTRIBUTION:
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U.S. GOVERNMENT PRINTING OFFICE: 1974

MEDDH-MR 10 July 1962

MEMORANDUM FOR THE RECORD:
SUBJECT: Use of Volunteers for Army Medical Research

1. Volunteers have been used by in-service and contract investigators for a great variety of research projects, since WW II. By and large research has been conducted in strict accordance with the Nuremberg Code of 10 rules drawn up following the Nuremberg trials.

2. Other than the Nuremberg Code, guidance for the conduct of human research has come from religious groups, such as a statement from the Pope in 1952; the declarations of Geneva and Rome, adopted by the World Health Association; requirements of National Medical Associations, including France, Britain and the U. S.; and the guarantees and standards recommended by the World Medical Association.

3. Federal agencies conducting or monitoring human research have operated under a variety of guidelines formulated from the Nuremberg Code and incorporating features from other agencies, as above and from specific regulations governing the particular service involved. All such guides have in common the safeguards put forth in the documents cited above and have resulted in research programs remarkably free from litigation.

4. The Army, specifically, has conducted both in-service and contract research involving the use of volunteers under rules which have been derived from the Nuremberg Code, the Army Organizational Act of 1950 (Sect 101) and Chief of Staff Memorandum 385, 30 June 1953 (Volunteers and Radiological, Biological and Chemical agents). On 12 March, 1954, principles, policies and rules of the Office of the Surgeon General: "Use of Human Volunteers in Medical Research" was published based on the foregoing. This has been the basic guide which has been followed since its publication, with minor changes or additions to apply to specific programs conducted at the various Army laboratories.

5. Adoption of an Act rather than continued reliance on the "Principles, Policies and Rules of the OTSG" has been needed to assure the Army that research done by or specifically for the Army will, when humans are involved, be monitored by the Surgeon General and will be in accordance with generally accepted principles.

6. Utilization of Volunteers in in-service programs:

a. Army Medical Unit, Fort Detrick. This has been a program remarkably free from difficulties. It has been conducted with the cooperation of the Seventh Day Adventists War Service Commission and has involved up to 200 volunteer subjects, annually. The SDA Commission has encouraged their young men to participate, and those who qualify are

selected at the MTC, Fort Sam Houston and transferred to the Walter Reed Unit where they perform non-combattant duty unless participating in experiments. It has been essential that the policies of the Medical Unit, Fort Detrick, be oriented toward defense against biological agents, and that work conducted have potential benefit to all mankind. This position has at times been difficult to maintain. Protocols for the use of biological agents or products, have in addition the unanimous approval of the Commission of Epidemiological Survey of the AFEB. Close liaison has developed during recent years with recognized leaders in the field of infectious diseases, ans particularly with the University of Maryland.

b. MRNL, Denver, Colorado. In January 1954, negotiations were begun with the Mennonite Central Committee to recruit young men for metabolic and nutrition studies. A metabolic ward was established and operations began later in the year. These volunteers are salaried, receiving $1,800.00 per annum and limited PX privileges as well as other privileges, such as recreational facilities, Red Cross, hobby shops, etc. The average tenure is 18 months, which fulfills Draft Board Requirements. This program has worked very well, however, there was one subject who, after release, sent an annual bill for treatment of ulcers. (It is noteworthy that the Mennonites have furnished thousands of young men to Federal and Private research programs in this country and in 39 foreign countries. The latest available figure is 4,300 as of 1960.) MNRL is cufrently authorized 10 such research spaces through a contract wihh the University of Colorado.

c. AMRL, Fort Knox. There are essentially no volunteers other than from members of the staff for specific experiments. Contracted research at the nearby University of Louisville is coordinated, however, and utilizes Medical students and other volunteers. Prior to the establishment of ARIEM, climatic tests were conducted and thermal stress pay was allowed.

d. ARIEM, Natick, Massachusetts, is newly organized. Subjects selected for heat and cold stressing remain with this unit as volunteers for long periods of time, and the nature of experiments is such that volunteers will usually remain only so long unless stress pay is allowed. An average of 30-40 volunteers are required, continually. The established codes of conduct of human experiments are rigidly enforced to prevent serious reactions.

e. U. S. Army Chemical Center, Edgewood, Maryland. Volunteers are recruited from various Army camps in U. S. Posters and bulletins inform the men that they may sign up for 30 days TDY and stress the importance and safety of the program. No special pay is offered but the volunteers do receive preferential treatment and passes if they are cooperative. Twenty to thirty are generally selected each month. In contrast to the ARIEM requirements, most volunteers for this program are subjected to short experiments and suffer with little discomfort.

f. WRAIR uses few volunteers, but programs, particularly in the Neuropsychiatry Division do occasionally require them. No special inducement has been a policy and local recruitment is generally adequate.

7. Contract use of volunteers: A complete survey of research contracts in which volunteers were used was conducted in 1960 prior to preliminary drafting of AR 70-25, 26 March 1962. At that time a total of 21 contracts were active. Approximately 3,000 students, 250 patients and 300 prisoners were participants. The general picture, today, is essentially unchanged. Investigators have utilized the 12 March, 1954 SGO Directive as a guide and have had prior approval of protocols by their own institutions, the project officer, the AFEB when applicable and appropriate Advisory Committees to the Surgeon General.

8. Problems concerning AR 70-25, March 1962.

a. para 1: A precise definition of Department of Army Research is needed.

b. para 6: Approval. Define "Major Command" and "other agency". Does the latter include direct submission by

the contractor or by the Med R&D, in this case? i.e.- the Project Officer submits the protocol for approval?

c. para 8: Implementing instructions.

1. What should content of implementing instructions be? To whom should they be sent?

2. To our laboratories the implementing instructions are simple: Protocols, particularly where CBR agents are used, must be submitted to Med R&D for approval @ DA level. This may be quite burdensome for Ft. Detrick.

3. Contractors position in this is less clear. Instruc- will have to be formulated for the guidance of project officers. All active contracts have been approved by TSA/R&D. Do those involving CBR already underway need to go to DA? What if DA turns down a project already contracted and paid for?

DONALD L. HOWIE
Lt. Colonel, MC
Assistant Chief
Medical Research

APPENDIX A

Volunteers: Reference Material in R&D Files

Following the publication of AR 70-25, 26 March 1962, it became obvious that this document would provoke many comments and inquiries both in and out of service. This represents a milestone, of sorts, in that it is the Official position of DA concerning this delicate subject. As such, it becomes a ruling subject to legal interpretation and application. The background is briefly outlined in the preceeding memo. Sources are:

1. AFEB Files: Contains basic correspondence in the formation of TSGO policy, March 1954 and statement by executive Secretary of AFEB on need for the policy, i.e.: "mandatory requirement for projects in classified areas requiring approval of the Secretary of the Army, but a guide for other types of research". There is also a minimum amount of correspondence concerning the necessity of all members of the AFEB to make certain that detailed protocols are submitted to TSGO when Army subjects are involved, and the drafts and copies of a directive "Information to be included in protocols submitted to TSGO in cases where Army Personnel are to be used as test subjects". A 1960 survey of all contractors using volunteers is included.

2. Prev. Med. Br. File: Materials, here, are largely those which pertain to the establishment of policies using Seventh Day Adventist volunteers at Fort Detrick. Materials date back through 1957, and include basic correspondence establishing immunization policies, recruitment (at BAMC), the policies of the SDA War Council, a history of the volunteer program at the Army Chemical Center and miscellaneous information concerning the position of the CES, AFEB, June 1960.

3. Deputy Director, R&D's File: Information dating back through 1957 on procurement of volunteers, orders assigning physicians responsible for volunteer studies, reprints on non-official reviews of volunteer research (Drug Research Reports reprint of Duke Law Journal, 1960, review; Dr. Beecher's AMA article 31 Jan, 19590. Materials here are sketchy.

4. Col Lee's File (Budget Branch): Correspondence, here is largely back through 1957. Included are: 1.) 1 Aug 57, Legal office opinion on 3rd person liability insurance under contracts.2.) The various categories of studies utilizing volunteers. 3.) 10 June '59 Drug Research reports review of National meeting on volunteer programs (Dr. Ladimer's review) which is excellent.4.) A copy of the 30 June 1953 C/S Memo: Use of volunteers in Research. 5.) Agreement and consent forms used in various programs. 6.) 1959 queries by Gen. Hays of the Navy and Air Force policies (no answers).

5. Personnel File (Mrs. Eyles): This is a more comprehensive file, with miscellaneous materials dating back to 1952: 1.) The draft and criticisms of AR 70-25 including those by McDowell, Tigertt, Benenson, Artiss, Col Vorder Bruegge. 2.) Reprints of articles previously mentioned, plus an excellent review in "science". 3.) History of the volunteer program at MRNL. 4.) Summaries of all research using volunteers as of Nov '60. 5.) Copies of legal opinions previously mentioned. 6.) Reports of other decisions, such as by the Catholic Church. 7.) The Ohio State Prison correspondence involving Gen Creasy -- a good demonstration of how touchy this subject really is. 8.) The documents on SDA participation. 9.) SOP's for AMRL volunteer programs.

6. Classified Files: Material in classified files is by and large referred to in the other files. References other than minor correspondence includes:

a. Original C/S Memo, 30 June '53 on use of volunteers, prior to declassification.

b. 12 Aug '54 letter from Col Wood clarifying and implementing above memo. Response of Ch Chml O attached.

c. 25 Feb '55 letter to TSGO from Legal division. Opinion on legal capacity to consent (ages 18-20) of troops.

d. 1955 correspondence series concerning Seventh Day Adventists, including letters from parents, legal council, advice of the SDA Council and responses of TSGO.

e. 11 April 1956 authorization for phychochemical studies -- staff action.

f. 18 May 1958 authorization to use V-agents and staff actions.

g. Legal implications of using women and children as subjects, 21 Oct 1959.

h. 13 Mar 59 designation of single physician as responsible. Legal opinion.

Pers-A212-mh
AUG 31 1962

NAV1.941006.061

THIRD ENDORSEMENT on NAVC, Phila, spdltr XG-4:EH:pao 7307 (4050) of 28 Aug 1962

From: Chief of Naval Personnel
To: Secretary of the Navy

Subj: Experimental studies of a medical nature involving persons in the Naval Establishment

1. Forwarded, recommending approval.

K. E. TAYLOR
ACTING ASSISTANT CHIEF FOR PLANS

Copy to:
NASA Hdqtrs., Wash. D.C.
NASA (MSC), Houston, Tex.
NAVAIRMATCEN (ACEL), PHILA
Chief, BuWeps
Chief, BuMed

7 Sept 62
Paul B. Fay, Jr.
Secretary of the Navy

RETURNED TO ORIGINATOR FOR DISPOSITION THIS DATE 9-10
SAF

4

SERIAL: 3941

4 1485

BUMED-711:mkf
31 Aug 1962

SECOND ENDORSEMENT on NAMC, Phil. spdltr XG-4:EH:pao 7307 (4050)
of 28 Aug 1962

From: Chief, Bureau of Medicine and Surgery
To: Secretary of the Navy
Via: Chief of Naval Personnel

Subj: Experimental studies of a medical nature involving persons in the Naval Establishment

Ref: (a) MANMEDDEPT, Chapter I, Section II, Article 1-11, "Experimentation of Personnel"

1. Forwarded, in accordance with reference (a), recommending approval.

2. The proposed study using human subjects will provide information not otherwise obtainable to validate specifications for the construction of manned space capsules. Test personnel will be subjected to increasingly high rates of negative G of very brief duration until discomfort levels are reached. The conditions of the experiment will be changed gradually, and test personnel will at all times be under the careful observation of trained Medical Department personnel. No injury to test personnel is expected to occur.

C. B. GALLOWAY
Assistant Chief for Research and
Military Medical Specialties

Copy to:
NASA Hdqtrs., Wash. D.C.
NASA (MSC), Houston, Tex.
NAVAIRMATCEN (ACEL), PHILA
Chief, BuWeps

4 1485

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C. B. GALLOWAY
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Military Medical Specialties

Copy to:
NASA Hdqtrs., Wash. D.C.
NASA (MSC), Houston, Tex.
NAVAIRMATCEN (ACEL), PHILA
Chief, BuWeps

4 1485

RAAE-13-972:MLJ

NAVAL LETTER

FIRST ENDORSEMENT on SecNav sndltr KG-4:EM:pao 7307 (4050) of 28 Aug 1962

From: Chief, Bureau of Naval Weapons
To: Secretary of the Navy
Department of the Navy
Washington 25, D. C.
Via: (1) Chief, Bureau of Medicine and Surgery
(2) Chief of Naval Personnel

Subj: Experimental studies of a medical nature involving persons in the Naval Establishment

Forwarded, strongly recommending approval. A BuWeps-BuMed-ACEL conference held 28 August evaluated the hazards and reviewed the procedures with the conclusion the work could and should be performed with no serious risk.

This data is necessary for future Navy systems involving negative g. If approved, this work will be performed at BuWeps Problem Assignment No. 005-AE13-16.

R. E. [illegible]
Assistant Chief for Research,
Development, Test and Evaluation

Copy to:
NASA Hdqtrs., Wash. D. C.
NASA (MSC), Houston, Tex.
NAVAIRMATCEN (ACEL), PHILA

4 1485

USE FOR URGENT LETTERS ONLY

DO NOT CLEAR THROUGH COMMUNICATION OFFICE

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☐ REGULAR MAIL ☐ SPECIAL DELIVERY

☐ AIR MAIL ☐ REGISTERED MAIL

CLASSIFICATION

UNCLASSIFIED - URGENT

IN REPLY REFER TO

NS-4:MEmpo
7007
(4039)

DATE 28 AUG 1962

TO: Secretary of the Navy
Department of the Navy
Washington 25, D. C.
Via: (1) Chief, Bureau of Naval Weapons
(2) Chief, Bureau of Medicine and Surgery
(3) Chief of Naval Personnel

(Fold)

NAVAL SPEEDLETTER—

Permits dispatch or informal language.

May be sent (1) with enclosures, (2) in a window envelope (size 8⅝" x 3⅝"), if contents are not classified as confidential or higher, (3) to both naval and nonnaval activities.

Is packaged 500 sheets of white or of one color: yellow, pink, or green.

Subj: Experimental studies of a medical nature involving persons in the Naval Establishment

This communication is a follow-up to NAVMAT Special Delivery, Unclassified-URGENT Ltr NS-4:MEmpo 7007 (4039) of 16 August 1962, which contained the same request as the present correspondence, but which is understood not to have been received by the Chief, Bureau of Naval Weapons.

Approval is requested to conduct the enclosed experimental study "Determination of the Effects of Impact, Negative Acceleration on Human Subjects" using volunteer personnel of the Naval Establishment as subjects. The enclosed study was formulated from the National Aeronautics and Space Administration (NASA) APOLLO Impact Conference held on 8 August 1962 and will provide information urgently required by NASA for the APOLLO program.

In view of the urgency expressed by NASA for the information to be obtained from this study, it is requested that approval be expedited.

By direction

Encl: (1) Determination of the Effects of Impact, Negative Acceleration on Human Subjects

COPY TO
NASA Hdqtrs., Wash., D. C.
NASA (MSC), Houston, Tex.

ADDRESS: Commanding Officer
Naval Air Material Center
Philadelphia 12, Pennsylvania

← SENDER'S MAILING ADDRESS

Address reply as shown at left; or reply hereon and return in window envelope (size 8⅝" x 3⅝"), if not classified as confidential or higher.

CLASSIFICATION

Unclassified - URGENT

NAVAL AIR MATERIAL CENTER
AIR CREW EQUIPMENT LABORATORY
PHILADELPHIA 12, PA.
Enclosure to NAVAL SPEEDLETTER NS-4:EH:mck 7307 (4050) dated 27 Aug 1962

DETERMINATION OF THE EFFECTS OF IMPACT, NEGATIVE ACCELERATION ON HUMAN SUBJECTS

Supine volunteer subjects dressed in coveralls shall be exposed to abrupt impact accelerations directed through the long axis of their bodies, from head to feet (negative acceleration). The Air Crew Equipment Laboratory (ACEL) Horizontal Accelerator shall be used to apply controlled acceleration-time patterns to the subject supporting structure. The latter shall consist of a rigid couch to which the subject shall be attached by a composite restraint harness with tie-downs located around each thigh, around the pelvis, around the chest and over the shoulders. The back of the couch shall be tilted to form an angle of 5 degrees between the seat back and the horizontal surface of the accelerator sled, so that the head portion of the couch shall be raised with respect to the hip portion. The couch shall be constructed so that an open angle of 107 degrees shall be maintained between the subject's thighs and torso and between his thighs and lower legs. A sufficient number of acceleration exposures shall be made using an anthropomorphic dummy to assure the adequacy of the support and restraint system before any human exposures are undertaken.

Accelerations shall be measured on the rigid structure of the couch supporting the subject. Present data on the performance of the ACEL Horizontal Accelerator indicates the following relationships:

Acceleration Level (G)	Velocity Change (ft/sec)	Onset Rate (G/sec)
.2	7.1	270
3.5	10.0	600
4	10.7	800
5	11.8	1000
6	13.4	1250
7	14.5	1500
8	15.1	1800
9	17.4	2000
10	18.8	over 2000
15	25.6	over 2000
20	32.4	over 2000

It should be noted that the above data were obtained from measurements made on the Accelerator Sled; considerable attenuation of the rate of acceleration onset can be anticipated with regard to what the subject may experience.

In no case will any subject be exposed more often than once in 24 hours to any acceleration level. It is planned to expose each of five subjects in succession to the following G levels on the dates indicated:

G Level	Date (1962)
2	6 September
3.5	7 September
5.2	8 September

4 1985

G Level	Date 1962
6.5	10 September
8.5	12 September
10.0	14 September
11.5	17 September
13.0	19 September
15.0	21 September
16.5	24 September
18.0	27 September
20.0	2 October

The G levels selected are arbitrary and will be modified in accordance with findings, as required. It is planned to prepare a summary of the data and findings by 5 October 1962.

A review of the literature on impact negative acceleration effects on humans showed only a limited amount of data to be available. From these data, properly restrained subjects have been shown to tolerate, without untoward effects, acceleration patterns having the following characteristics: less than 10 G level, less than 100 G/sec onset rate, and less than 30 ft/sec velocity change. Reference is made to Air Force Pamphlet AFP 160-10-4 entitled "Physiology of Flight" of 1 January 1961 which indicates a tolerance level for downward ejection of 16 G at 200 G/sec, although the original source of this information is not given. Exposure of chimpanzees to impact transverse accelerations (both forward and rearward facing) indicates survival without injuries to patterns having 2 to 3 times the peak G and onset rates of those tolerated by humans. Chimpanzees tolerated impact negative acceleration patterns of 26 to 51 peak G, 700 to 1000 G/sec onset rates and durations of 0.13 to 0.20 sec. Applying the same factor of 2 to 3 to peak G and onset rate, it would appear that the tolerance limits for humans described above are validated by comparable animal experiments. No systematic investigations have been reported with respect to negative impact accelerations applied to living organisms which would indicate the combined effect of various combinations of onset rates, G levels and velocity changes.

Exposure of subjects using the method and equipment described above shall be done with the utmost care and caution. An attending flight surgeon shall personally monitor the condition of the subjects throughout the study, and shall determine when and if a given subject shall be exposed at any particular time to impact acceleration. The full diagnostic and clinical facilities of the Philadelphia Naval Hospital are available and shall be utilized as deemed necessary. Sufficient information shall be obtained prior to the study on the normal physical condition of the subjects (including X-rays of the spine and skull, and electroencephalograms) so that changes which may occur can be detected before they lead to serious or irreversible sequellae. In no case will a subject be exposed to the test conditions when he is unwilling or expresses appreciable discomfort. Continuous electrocardiograms, before, during and after each exposure, shall be obtained, and such other procedures shall be followed to gain information regarding the subject's condition as are considered appropriate by the attending flight surgeon. Approach to more severe exposure conditions will be made cautiously, with close medical monitoring and repeated assessments of the safety and well-being of the subjects. Procedures outlined in Article 1-11, Manual of the Medical Department, 1962, shall be fully complied with.

CIA-0206485-A
140-83

DRAFT

29 May 1963

MEMORANDUM FOR : THE RECORD

SUBJECT : MKULTRA, Subproject 140

1. The purpose of this subproject is to provide for the continuation of investigational programs involving utilization of human volunteer subjects and the services of [redacted]

2. This program is designed to exploit clinical, laboratory and institutional facilities as well as professional knowledge in providing answers to specific questions and solutions to specific problems of direct interest to the Agency. This subproject will permit the utilization of the professional services of [redacted] who is located in [redacted]

3. The scope of [redacted] services will include the following:

a. Consultation with TSD on programs of technical interest.

b. Maintain an investigational cover activity for backstopping and use in conducting clinical evaluation and feasability trials of interest to TSD.

c. On request, assist in designing experimental

protocols and conducting, under controlled conditions, pharmacological and clinical tests in human volunteers of specific chemicals, biochemicals, and biologically active materials of direct interest to the Agency.

d. Perform professional services on request.

4. The proposal indicates the nature of the investigational program being used for cover purposes. In addition, pharmacological and clinical investigations of Agency interest will be conducted; these investigations will encompass clinical testing and feasibility testing of drugs affecting human behavior. Other activities will include assessment and feasibility studies on covert marking systems. Seriological and human blood group identification systems will be assessed to determine their feasability.

5. The funds for this project will be transferred directly. [redacted] will be reimbursed for expenses and professional services rendered.

6. The cost of this program for a period of one (1) year beginning 1 April 1963 will not exceed $20,000.00. Charges should be made against Allotment No. 3125-1390-3902.

7. The principal investigator will submit invoices and be reimbursed accordingly.

8. It is not anticipated that any permanent equipment will be

140-15

required for the program.

9. It has been agreed that documentation and accounting for travel expenses which are reimbursable shall conform to accepted practices.

10. It is agreed that technical reports reflecting the progress of the activities will be submitted at mutually acceptable intervals.

11. [redacted] holds a Top Secret Agency approval. The Project will be unclassified.

Chief
TSD/Biological Branch

Distribution:
Original only

Attachment:
Proposal

ARMY REGULATIONS
No. 10-37

HEADQUARTERS,
DEPARTMENT OF THE ARMY
WASHINGTON, D.C., *12 August 1963*

MEDICAL SERVICE

RADIOISOTOPE LICENSE PROGRAM (HUMAN USE)

Section I. GENERAL

1. Purpose and scope. *a. Purpose.* These regulations—

(1) Prescribe policies and procedures for the human use radioisotope license program.

(2) Establish the procedure for the reporting of radioisotopes in human use activities.

(3) Furnish guidance to major oversea commanders whose medical treatment facilities outside the United States are authorized to operate human use radioisotope programs without the requirement for a license from the U.S. Atomic Energy Commission.

b. Scope. These regulations—

(1) Apply to all Army medical treatment facilities located in a State or territory of the United States, the District of Columbia, or the Commonwealth of Puerto Rico.

(2) Apply to major oversea commanders as follows:

(*a*) Applies to installations and activities assigned to major oversea commanders which are located in an area which falls under AEC jurisdiction.

(*b*) Major oversea commanders will adopt such portions of these regulations for installations and activities outside the United States as are necessary to insure the continuity of professional qualifications and maintenance of current documentation of the training and experience of the individual radioisotope user. (This official record of professional qualifications must be acceptable to The Surgeon General and the U.S. Atomic Energy Commission when an individual is reassigned to the United States or that geographical area where radiological byproduct materials are licensed by the U.S. Atomic Energy Commission.)

(3) Do not apply to the use of equipment generating ionizing radiation by electrical means for diagnostic or therapeutic procedures. The provisions of TB MED 62 (*Diagnostic X-Ray Protection*) apply for use of diagnostic X-ray equipment.

2. Definition of terms. For the purpose of these regulations, the following definitions apply—

a. Byproduct materials. Means any radioactive material (except special nuclear material) yielded in or made radioactive by exposure to the radiation incident to the process of producing or utilizing special nuclear materials.

b. Special nuclear material. Plutonium, uranium 233, uranium enriched in the isotope 235, or

Incl 2

any other material which the U.S. Atomic Energy Commission determines to be special nuclear material.

c. Sealed sources. Any radioactive material that is inclosed, or is to be used in, a container in a manner intended to prevent leakage of the radioactive material or any of its daughter products.

d. Human use. The internal or external administration of radioactive material (byproduct material or otherwise) or the radiation therefrom, to human beings.

e. License. A license issued by the U.S. Atomic Energy Commission.

3. **Responsibilities.** *a. The Surgeon General.* The Surgeon General is responsible for staff supervision of this program and administrative approval of licenses pertaining to human use of radioactive material. He will specifically—

(1) Designate medical treatment facilities authorized to use radioisotopes for human use and provide diagnostic and/or therapeutic radioisotope services.

(2) Provide policy guidance and advisory support to Army medical treatment facilities.

(3) Review all license applications for human use of radioisotopes.

(4) Maintain a current list of approved individuals (users) and radioisotopes for which the users are approved.

(5) Plan for a long-range scientifically oriented and integrated program which incorporates realistic requirements for training, construction, and equipment.

(6) Perform, at least on an annual basis, a survey of all aspects of radioisotope activities at licensed medical treatment facilities.

(7) Appoint a Radioisotope Committee to assess the program by evaluating the minutes in the letter reports of medical treatment facilities using radioisotopes, submitted in accordance with paragraph 4, survey reports and other available data.

b. Major overseas commanders, ZI army commanders, Commanding General, Military District of Washington, U.S. Army; Commanding General, U.S. Army Materiel Command, and other separate commanders having primary responsibility for research and development projects, or technical operations. These commanders will be responsible for insuring that commanders of all installations and activities under their jurisdiction—

(1) Are provided with the proper authorization, including valid AEC license when applicable, prior to procuring or using radioactive material or sources of ionizing radiation for the purpose of radiation exposure of human beings (volunteers or otherwise), associated with military projects.

(2) Are provided with adequate means and procedures for safe handling of radioactive materials.

(3) Have acquired a written approval from the Secretary of the Army (AR 70-25, 26 March 1962), prior to the submission of license application for human use, when volunteers are to be used as experimental research subjects.

c. The commander of each medical installation or treatment facility. This commander is responsible for all aspects of the radiation program within his command. This responsibility includes, but is not limited to, the following:

(1) Insure that the medical treatment facility concerned has been assigned the mission by The Surgeon General to provide diagnostic and/or therapeutic radioisotope services.

(2) Insure that the medical treatment facility as the applicant for an AEC license, or as a licensed medical treatment facility provides adequate support for the human use activity to include—accommodations for clinical care of patients; availability of suitably trained and experienced personnel; availability of proper equipment such as handling devices, shields, measuring and monitoring instruments; and standardized operating procedures for the protection of health and safety in all aspects of the medical treatment facility operation.

(3) Appoint a radioisotope committee which will be designated as user on the license of the medical treatment facility.

(4) Insure that the individual users of radioisotopes within the facility and each ra-

dioisotope used will be approved and controlled by the Radioisotope Committee as the licensed user in accordance with requirements as specified in licensing procedures and regulations of the U.S. Atomic Energy Commission (title 10, Code of Federal Regulations and RC 12 "The Medical Use of Radioisotopes—Recommendations and Requirements by the Atomic Energy Commission").

(5) Review radioisotope program and submit reports and data in accordance with paragraph 4.

(6) Insure that each user's 201 file reflects current qualifications of the individual user, and that this information remains a permanent portion of that file.

(7) Performs within reason or permits the U.S. Atomic Energy Commission to perform such tests or inspections as the Commission deems appropriate or necessary for the administration of their regulations on radioisotopes.

d. Radioisotope Committee. This committee will consist of the Chief of Medicine, the Chief of Pathology, the Chief of Radiology, the Chief of the Radioisotope Clinic, and a radiation protection officer or health physicist. A nonvoting member of supply and service is mandatory. Others may be included at the discretion of the medical treatment facility commander. At medical treatment facilities with limited qualified personnel, the radioisotope committee will conform to stated composition to the extent that personnel permit. Under this circumstance, one individual on the committee may serve in a dual capacity. This committee will have the following responsibilities:

(1) Review and grant permission for, or disapproval of, the use within the medical treatment facility of byproduct material from the standpoint of radiological health and safety and other factors established for medical use of these materials.

(2) Certify individual users for each type of procedure with each individual radioisotope and insure that a copy of such certification is placed in the appropriate users' 201 file.

(3) Prescribe special conditions which may be necessary to include, but not limited to, medical examinations, additional training, designation of radiation areas, location of radioisotope use, waste disposal method, and protective measures for personnel in care of patients.

(4) Review records and receive reports from the radiological protection officer or other individuals responsible for health and safe practices.

(5) Recommend corrective actions when indicated.

(6) Keep an official record of its actions.

(7) Maintain current records of the training of approved users, documenting the qualifications and limitations of each.

(8) Maintain data for the report required by paragraph 4.

4. Reporting requirements. The following reports will be prepared:

a. Radioisotopes in Human Use Activities, RCS MED-197. Commanders of each medical treatment facility located in the United States and the Commonwealth of Puerto Rico having diagnostic or therapeutic radioisotope service will prepare the report covering the period of each calendar quarter. Report will be in narrative form and will be dispatched through command channels to The Surgeon General, Department of the Army, ATTN: MEDPS PO, Washington, D.C., 20315, by the 15th working day following the close of the report period and will contain at least the following information:

(1) Copy of the minutes of each radioisotope committee meeting, including a record of all actions taken by the committee. Special care should be taken to include formalized actions that—

(*a*) Certify each individual for each new use of radioisotope.

(*b*) Appoint a radiation protection officer.

(2) Copy of the training and experience record of each individual who is an approved user of radioisotopes (AEC Form 313a, page 3) or appointed a radiation protection officer. After initial record is submitted, subsequent report will include any changes in qualifications or in certification during the report period.

(3) Notification of all changes in membership of radioisotope committee. Each new member of the radioisotope committee will be documented as to specific training and experience.

(4) Quantities of radioisotopes procured, used (exclusive of volunteer RD activities), and disposed of during the period and in storage end of period.

(5) List of procedures with dosage for each radioisotope used during the period, that varies from the dosage range listed in table I of the appendix.

(6) Information on unsolved problems, new or improved developments, or comments on the support rendered by The Surgeon General.

b. Radioisotopes in Human Use—Volunteer RD activities. RCS MED-198. Individuals or the commanders designated as a licensee for a research and development project which utilizes any radioisotopes in human use volunteer activities located in the United States and the Commonwealth of Puerto Rico on completion of the project will prepare a final narrative report consisting of—

(1) The human use component of the project to include, but not be limited to, a description of the volunteers, as to source, age, sex, and number.

(2) Procedures used.

(3) Dosages involved, and

(4) Evaluation of the total integrated lifetime dose received by each individual prior to and following the experiment. Report will be submitted through command channels to The Surgeon General, ATTN: MEDPS-PO, Department of the Army, Washington, D.C., 20315, within 45 calendar days after completion of the project.

5. License applications. Applications for byproduct material license for human use will be submitted on AEC Form 313 (Application for Byproduct Material License, Supplement A Human Use) in sufficient numbers so that six copies (all signed and dated) are received by The Surgeon General.

a. Class II medical installations and activities will submit such applications direct to The Surgeon General, ATTN: MEDPS-PO.

b. Class I medical installations will submit applications through command channels to The Surgeon General, ATTN: MEDPS-PO.

c. Commanders responsible for specific research and development projects which require licenses involving the human use of radioactive materials, that are disassociated from medical treatment facilities, patient care, or diagnostic or therapeutic care, will submit license applications through command channels to The Surgeon General, ATTN: MEDPS-PO. Adequate supporting documentation covering the training and experience of personnel involved, SOPs, plans, and other pertinent data is essential to process the application. Direct correspondence with the Atomic Energy Commission in license applications is not authorized, except to reply to correspondence initiated by AEC; information copies of all such correspondence will be forwarded by the commander concerned to The Surgeon General, ATTN: MEDPS-PO. The use of improper channels will result in considerable delay since AEC will return the application to the applicant pursuant to agreement with The Surgeon General. Guidance to the applicant in completing license application is provided in section II.

6. Procurement of Atomic Energy Commission regulations and forms. Supplies of the Atomic Energy Commission regulations and blank forms pertaining to the use and licensing of byproducts, special nuclear or source material may be obtained upon request from the U.S. Atomic Energy Commission, Division of Licensing and Regulation, Washington, D.C., 20545.

TAGO 207A

Section II. INSTRUCTIONS FOR COMPLETING LICENSE APPLICATIONS

(Item numbers keyed to format block numbers of AEC Forms 313 and 313a)

7. Form AEC 313 (Application for Byproduct Material License).

a. Item 1(a) Name and Street Address of Applicant. Enter name and address of facility.

b. Item 1(b) - Street Address(es) at Which Byproduct Materials Will Be Used. Self-explanatory.

c. Item 2 Department To Use Byproduct Material. List all departments where isotopes may be used.

d. Item 3 Previous License Number(s). Self-explanatory.

e. Item 4 Individual User(s). Enter statement, "Users will be approved by the Radioisotope Committee."

f. Item 5--Radiation Protection Officer. Enter statement, "This officer will be appointed by the Radioisotope Committee." This officer will be the best qualified individual available and his duties are to be specifically assigned. Subsequent changes in personnel must be reported to The Surgeon General in accordance with provisions of paragraph 4, giving qualifications of the replacement.

g. Item 6(a) Byproduct Material. Enter statement "See inclosure _____." List of acceptable radioisotopes for human use, see table I.

h. Item 6(b)- Chemical and/or Physical Form and Maximum Number of Millicuries of Each Chemical and/or Physical Form that You will Possess at Any One Time. Enter any item which has been established by adequate medical research and can be supplied by an approved medical drug corporation. Each isotope should be included in and not exceed that quantity listed in table I unless previously licensed or justified through correspondence with The Surgeon General, ATTN: MEDPS PO.

i. Item 7 - Describe Purpose for Which Byproduct Materials will be Used. Enter statement "See supplement A (Form AEC 313a)."

j. Item 8 --Type of Training and *Item 9--Experience With Radiation.* Initially the training of the members of the Radioisotope Committee will be submitted. Subsequent changes in personnel of isotope committee will not require an amendment to license but must be reported to The Surgeon General giving qualifications of the replacement. See paragraph 4.

k. Item 10 - Radiation Detection Instruments. List available instrumentation. Sophisticated instruments of a medical diagnostic type must be available. Survey instruments of a low-level capability must also be present for conducting surveys of the clinic for contamination. These survey instruments must be calibrated at least every 6 months and after each maintenance procedure or battery change. The calibration should include a check of at least 2 points on each scale. Use of check sources included with instruments does not constitute a calibration. High range instruments must be available for high level gamma emitters such as Gold 198 and Iodine 131 (IM 108, not acceptable).

l. Item 11--Method, Frequency, and Standards Used in Calibrating Instruments Listed Above, Item 12--Film Badges, Dosimeters, and Bio Assay Procedures Used, and *Item 13--Facilities and Equipment.* Self-explanatory.

m. Item 14--Radiation Protection Program. A detailed standard operating procedure will be submitted describing methods of control, functions, and membership of the Radioisotope Committee, operation of radioisotope procurement, use and disposal, protection program and control. Individual names will not be used in the development of this SOP but responsibilities must be assigned by military or civilian position. Considerable time and correspondence have been occasioned in the past reviews of license applications due to lack of program coordination or documentation in the following areas:

(1) *Wipe testing.* This is required on all sealed sources every 6 months. A person must be designated by position who will be responsible for the performance of the wipe test. He must have adequate training and knowledge to know how to perform such a test safely. Procedures for performing the test must be given and an instrument with the capability of detecting 0.005 microcuries of activity must be available for counting. Strontium 90

beta applicators are considered as sealed sources.

(2) *Logs and records.*

(*a*) AEC Form 3 (Notice to Employees—Standards for Protection Against Radiation) must be posted in a conspicuous location.

(*b*) AEC Form 4 (Occupational External Radiation Exposure History) and Form 5 (Current Occupational External Radiation Exposure) must be maintained. This record should also be entered on DD Form 1141 (Record of Exposure to Ionizing Radiation) in accordance with AR 10-131.

(*c*) The license and the facility SOP must be posted or readily available.

(*d*) Inventory must be maintained of each radioisotope received, used, lost through decay, or disposed of. Periodic inventory balance will be determined at frequent intervals, depending upon the magnitude of the half-life of the isotope in use, such as monthly for Iodine 131. DA Form 8-212 (Narcotic and Controlled Drug Record) may be adapted for this purpose.

(*e*) Wipe tests records will be kept on a consecutive entry log and the removable activity must be recorded in microcuries.

(*f*) Instrument logs must be maintained indicating calibration and maintenance.

(*g*) Results of surveys must be maintained.

(3) *Signs, labels, and barriers.* Isotopes must be labeled with the radiation sticker of yellow and magenta, and the isotope and activity as of a certain date per cc or unit must be recorded on the label. The storage area should be neat and segregated by type. Gamma emitting isotopes must be so stored that the radiation level at the edge of the storage area does not exceed 2 mr/hr. A large sign "Caution—Radioactive Material" must be posted at the storage area (Title 10, Code of Federal Regulations (part 20), and AR 385-30).

(4) *Marking controlled area—when Gamma emitters are used for therapy.* Any activity in excess of 2 mr/hr in a potentially occupied area is considered to be a controlled area and will be marked with appropriate signs or symbols ((3) above). The radiation at the skin surface of the patient will be measured and recorded so that nursing and other appropriate personnel can be properly advised regarding instituting their activities in close association with the patient. Nurses and others caring for this type of patient should be informed of the hazards of radiation and monitored by film badges or dosimeters. Visitors should be warned of the radioactive material and should be restricted to an area below 2 mr/hr. Lead shielding may be required. If the dose rates in rooms adjacent to the patient are equal to, or above 2 mr/hr, these rooms should not be occupied by patients.

n. Item 15 Waste Disposal. Wastes may be disposed of by holding and permitting complete decay, then disposal of the no longer active material. Liquid wastes may be disposed of through the sanitary sewer providing the requirements of the Code of Federal Regulations, title 10, part 20, are met. Solid radioactive wastes cannot be buried or burned without special permission. Disposal should be in accordance with AR 755-380. Title 10, part 20, Code of Federal Regulations states that AEC approval must be granted before disposal of radioactive material by incineration. To secure approval, the applicant must provide the following information:

(1) The type, quantity, and chemical form of byproduct material to be incinerated.

(2) The method of measurement of, or estimation of, the concentration of radioactive material in the effluent at the point it leaves the stack.

(3) Methods of control to insure that particulates and concentrations of radioactive materials are not released which could result in exposures of individuals in excess of the levels set forth in AEC's "Standards for Protection Against Radiation," Part 20.

(4) The height of the incinerator stack, expected dilution factors (if necessary) and the height of and distance to buildings in the surrounding area.

(5) The procedures which will be followed to prevent overexposure of personnel dur-

ing all places of the operation, particularly the instructions given to the persons handling the combustibles and the ashes.

(6) The method for disposing of contaminated ash. An example of an approved action is as follows:

Example: The anticipated activity to be used at any one time for metabolism studies will not exceed 30 microcuries of Carbon 11. Waste inherent in such experimental procedures will include for the most part absorbent paper used to contain accidental spills and that paper used for wiping pipette tips, etc. At times laboratory animal carcasses will be included in this type of radioactive waste particularly desirable to incinerate.

Combustion will take place in a closed brick-type furnace at the sewage plant using both methane from sewage gas and natural gas. The temperature ranges from 1200° to 1400° F. and will remain constant for a period of nearly 24 hours to insure complete combustion. The radioactive waste will be mixed with both dry and wet nonradioactive waste in sufficient volume so that concentrations of effluents will not exceed the amount as specified in the National Bureau of Standards Handbook 53 or part 20, appendix B, table II, Code of Federal Regulations. However, the anticipated activity to be incinerated should not exceed a total of 5 to 10 microcuries per week except for an occasional small animal carcass. Depending on the activity of the waste, incineration will occur once weekly.

a. Item 16—Certificate. The license is always for the facility, therefore all copies will be signed either by the commandant or executive officer.

8. Form AEC 313a (Application for Byproduct Material License—Supplement A—Human Use). *a. Item 1(a)—Using Physician's Name* and *Item 1(b) Name and Address of Applicant.* Enter the facility, name, and address.

b. Item 2 License of the Using Physician and *Item 3 A Statement of the Using Physician's Clinical Radioisotope Experience.* Enter statement, "Not applicable."

c. Items 4(a), (b), (c), and (d) Proposed Diagnosis or Treatment. This should be completed for all accepted isotopes and uses.

d. Item 5 Proposed Dosage Schedule. Proposed dosage range for each specific condition to be diagnosed or treated is listed in table I. Any dosage which exceeds accepted dosage levels must be fully explained. Local radioisotope committee will not approve dosage levels in excess of published levels without prior approval of The Surgeon General.

e. Item 6 If Byproduct Material Will Not Be Obtained in Pre Calibrated Form . . ., Describe Identification, Processing, and Standardization Procedures. Self explanatory.

f. Item 7 The Proposed Use of Byproduct Material Has Been or Will Be, Approved by the Medical Isotope Committee. Enter Statement, "Yes."

g. Item 8 Hospital Facilities for Individual Practice Use Only. Enter statement, "Not Applicable."

h. AEC Form 313a, page 3. This form will be completed and submitted on all individuals and demonstrate approval by the Radioisotope Committee. Resubmission of page 3 addressed to The Surgeon General (par. 4), is required when the individual is certified in a new use of, or a new radioisotope. The resubmission does not require an Atomic Energy Commission amendment to the license.

APPENDIX

RADIOISOTOPE COMMITTEE

The Radioisotope Committee as user of facility license should select from Table I, below, those radioisotopes, usages, etc. that are practical for current as well as planned operations after considering assigned mission, facility, personnel, and types of consultants available to the facility. It is not intended that facility license be restricted to radioisotopes based on current training status of assigned personnel. It is intended that license be broad enough in authorization to allow the Radioisotope Committee to procure isotopes for, or remove isotopes from, licensed program dependent upon availability of trained personnel to the facility without amending license as individual users or consultants arrive or depart.

a. License applications which include additional radioisotopes for human use or deviations in excess of the limits (table I) will require special documentation as to need, method of use, control, etc. for those conditions peculiar to each medical treatment facility.

b. Human use radioisotopes that do not require AEC license to utilize, will not be listed on license application, but will be submitted to The Surgeon General by letter, with appropriately developed program. These materials will be controlled by the Radioisotope Committee with comparable procedures as applicable to licensed radioisotopes. Examples of nonlicensed material are—accelerator produced radioisotopes such as Sodium 22, Cobalt 57; or natural items such as radium or thorium.

c. Radioisotopes not used in human use program but intended for animal research will be identified as such on the same license and controlled by the same Radioisotope Committee. Radioisotopes for animal research will require separate documentation of the proposed operational program including data as to available personnel, facilities, controls, waste disposal, etc. for each independent use.

d. Sealed sources, calibration sources, instrument check sources, etc. that are an integral part of medical treatment facility programs will be included on the same license application but must be designated as a component part of the control program with information as to its use and care.

Table I. Acceptable Radioisotopes for Human Use

(As of February 1963)

		Diagnostic Studies	*Dosage range*	*Authorized on hand*
				10 mc
I-131	NaI	Sodium Iodide	10-15 μc	
		(Thyroid uptake)	30-100 μc	
		(Thyroid scan)	250-500 μc	
		(Checking metastases, thyroid cancer)		5 mc
I-131	RISA	Radio Iodinated Serum Albumin	5-10 μc	
		(Plasma Volume)	200 250 μc	
		(Brain tumor localization)	20 μc	
		(Cardiac output)		2 mc
	Hippuran		5-10 μc	
		(Renogram)		2 mc
	Rose Bengal		350-500 μc	
		(Liver scan)	10-20 μc	
		(Liver function)		1 mc
	Oleic Acid		25 μc	
		(Fat absorption)		1 mc
	Triolein		25 μc	
		(Fat absorption)		2 mc
	Cholografin (Iodipamide Sodium)		25 μc	
		(Gall bladder function)		

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TAGO 207A

Table I. Acceptable Radioisotopes for Human Use—Continued

		Dosage range	Authorized on hand
I 125	NaI—Sodium Iodide		1 mc
	(Thyroid uptake)	5–15 μc	
	(Thyroid scan)	20–80 μc	
	RISA—Radio Iodinated Serum Albumin		1 mc
	(Plasma Volume)	5–10 μc	
	Hippuran		1 mc
	(Renogram)	2–4 μc	
Cr-51	Na_2CrO_4—Sodium Chromate		3 mc
	(Rel cell mass)	25–35 μc	
	(GI Bleeding)	50–75 μc	
	(Rel cell survival)	50–75 μc	
	$CrCl_3$—Chromic Chloride		1 mc
	(Plasma volume)	10 μc	
Co-57 or Co-58 or Co-60	$CoCl_2$—Cyanocobalamin (B_{12} Co^{57})		10 μc
	(Schilling test)	0.5 μc	
	(Schilling test)	0.5 μc	
	$CoCl_2$—Cyanocobalamin (B_{12} Co^{60})		
	(Schilling test)	0.5 μc	
Gold-198	$AuCl_3$—Colloidal Gold		25 mc
	(Liver scan)	70–100 μc	
Iron-59	$FeCl_3$—Ferric Chloride		0.5 mc
	(Iron turnover study)	10–15 μc	
	—Ferrous Citrate		0.5 mc
	(Iron turnover study)	10–15 μc	
Hg 203	Chlormerodrin		10 mc
	(Kidney scan)	100–150 μc	
H3	H_2O—Tritiated Water		25 mc
	(Total body water)	1–2 mc	
Na24	NaCl—Sodium Chloride		1 mc
	(Total exchangeable sodium)	50–100 μc	
	Therapeutic Uses		
I 131	NaI—Sodium Iodide		250 mc
	(Hyperthyroid)	5–10 mc	
	(Thyroid carcinoma)	100–150 mc	
	(Cardiac disease)	5–30 mc (accumulation)	
Au-198	$AuCl_3$—Colloidal Gold		250 mc
	(Malignant effusions)	100–150 mc	
	(Prostate cancer)	25–100 mc	
P-32	Na_2HPO_4—Sodium Phosphate		25 mc
	(Leukemia)	5–10 mc	
	(Polycythemia Vera)	5–10 mc	
	$CrPO_4$—Colloidal Chromic Phosphate		
	(Malignant effusion)	5–10 mc	
	Laboratory Tests		
	Triiodothyronine (T-3)		1 mc
	(In vitro RBC uptake)	0.25–0.5 μc	
	Sealed Source		
Sr-90	$SrCl_2$—Strontium Chloride		25 mc
	(External therapy, sealed source)		

[MEDDS-P]

By Order of the Secretary of the Army:

EARLE G. WHEELER,
General, United States Army,
Chief of Staff.

Official:
J. C. LAMBERT,
Major General, United States Army,
The Adjutant General.

Distribution:
Active Army: To be distributed in accordance with DA Form 12-9 requirements for DA Regulations—Medical Service C.
NG: None.
USAR: None.

TAGO 207A

U.S. GOVERNMENT PRINTING OFFICE: 1961

708449

OFFICE MEMORANDUM

TO : Distribution September 3, 1963

FROM : T. L. Shipman, M.D., Health Division Leader

SUBJECT: ADMINISTRATION OF TRACER DOSES TO HUMANS FOR EXPERIMENTAL PURPOSES

SYMBOL : H

In a memo dated July 12, 1956, I established the ground rules which would, of necessity, be followed in all experimental procedures involving the administration of tracer doses of radioactive isotopes to human volunteers. I would here like to restate these rules:

1. Each experiment which requires the administration of tracer doses to human volunteers must have the written approval of the Health Division Leader or his Alternate.

2. The request for such approval must contain a statement as to the maximum dose to be administered, together with a statement as to the maximum permissible dose for such material.

3. All subjects will be bona fide volunteers who are fully informed as to the procedure to be carried out.

4. The administration of any such doses shall be carried out only under the immediate and direct supervision of a physician licensed to practice medicine in the State of New Mexico.

The only thing which has changed since this SOP was prepared is the fact that for the first time since 1947 Group H-4 will not have a licensed physician on its staff. For this reason it will be necessary if any such work is to be done to request the collaboration of the physicians on the staff in Group H-2. It is particularly important that section 4 above be followed to the letter in the event of any subcutaneous or intravenous administration of all materials.

Generally speaking, Wright Langham has blanket authority to approve or disapprove such procedures, although all proposals in any way out of the ordinary have been discussed with me.

Section 2 above, however, must be carried out with each proposal for experiments involving humans with the required statement kept on file in the H-4 Group Office.

T. L. SHIPMAN, M.D.
Health Division Leader

TLS/de

Distribution: Wright H. Langham, H-4
Group H-4 Section Leaders
Harry O. Whipple, M.D., H-2
Paul L. Flynn, M.D., H-2
Duane Drake, M.D., H-2

00131781.002

1055170

DEPARTMENT OF THE NAVY
Bureau of Medicine and Surgery
Washington, D.C. 20390

BUMED 6710.49
BUMED:3113:apl
5 February 1964

BUMED INSTRUCTION 6710.49

From: Chief, Bureau of Medicine and Surgery
To: Naval Hospitals

Subj: Investigational drugs; guidelines for handling

Ref: (a) MANMED arts. 1-11 and 1-12

1. Purpose. To provide guidelines for the safe handling of investigational drugs, and to minimize the chance for misadventure in their use.

2. Definition. Investigational drugs are those new drugs, including vaccines and biologicals, not released for general use and not cleared for sale in interstate commerce by the Federal Food and Drug Administration.

3. Statement of Principles. Following is a resume of a Statement of Principles Involved in the Handling of Investigational Drugs. The Statement was approved by the American Hospital Association, the American Society of Hospital Pharmacists, and the American Nurses Association.

a. Since hospitals are the primary centers for clinical investigation of new drugs, the hospitals and the medical staffs have an obligation to their patients to see that proper usage procedures are established.

b. Investigational drugs should be used only under the direct supervision of the principle staff investigator, who should assume the burden of securing the necessary consent and assuring that such investigations are performed in strict compliance with Part 130.3 of the New Drug Regulation under the Federal Food Drug and Cosmetic Act. Consent of the patient will be required also to release the name or other privileged information to any other agency or to any sponsor and use of case numbers or other coding is preferable. Chapter 23, MMD is applicable. (In all cases, BUMED approval for the use of investigational drugs must be obtained as provided by reference (a). In urgent cases, BUMED authorization may be obtained by telephone or wire, ATTN: Director, Professional Division, Area Code 202, Oxford 6-1280, during normal working hours or BUMED Duty Officer, Area Code 202, Oxford 6-2063, outside normal working hours.

c. The hospital should do all in its power to foster resea... consistent with adequate safeguard for the patient.

d. Nurses who administer investigational drugs should be provided with such basic information as dosage forms, strengths availa actions and uses, side effects, and symptoms of toxicity.

e. The hospital should establish a central location to maintain and make available essential information on the drugs.

f. The pharmacy service should store the drugs and provide for their proper labeling and dispensing in accord with the investigator's written orders.

4. Guideline Procedures. The following procedures should be adopted for the control and use of investigational drugs, with any modifications necessary to meet the individual needs of the hospital:

a. Requests for use of the drugs shall be approved by a pharma and therapeutics committee or a clinical research committee prior to submission to BUMED for final approval.

b. The drugs shall be shipped directly from the manufactu in the name of the investigator, to the pharmacy, to assure sa keeping under proper storage and for record procedures.

c. Upon receipt, the pharmacy staff, with the assistance of the investigator, shall prepare a NAVMED 1448, Investigational Drug Data Record.

d. The pharmacy shall attach to each container a distinctive label (color or shape) containing the statement "Investigational Drug - Not for General Use" and the name of the drug (or if a code number is used, then the pharmacological classification; for examp "Analgesic Drug" or "Antihistaminic Drug").

e. The pharmacy shall allocate a separate locked area for the exclusive storage of the drugs.

f. The principal investigator, or any authorized doctor desig nated by him, shall request the drug from the pharmacy by means of a prescription form.

g. The prescriptions shall be kept in a separate file, number consecutively, and the number prefixed by "ID".

h. A separate NAVMED 1449, Investigational Drug Inventory and Prescription Record, shall be maintained in the pharmacy for each drug. This provides a perpetual pharmacy inventory and serves as a ready reference of all patients receiving the drug.

i. When the drug is delivered to the ward, a completed copy of the NAVMED 1448, Investigational Drug Data Record, and a NAVMED 1398, Narcotic and Controlled Drug Data Record, shall be delivered to the ward nurse and a receipt shall be obtained. This will assure strict accountability and a perpetual inventory for all drugs on the wards. Nursing personnel shall be responsible for returning unused drugs and the completed NAVMED 1398 to the pharmacy and for initiating requests for additional supplies of the drug from the pharmacy.

j. The pharmacy shall dispose of (by return to the manufacturer or by destruction, as most feasible) all drugs no longer in use or for which future use is not anticipated.

k. If "double blind" studies are utilized, the place for the code shall be in the pharmacy.

5. Availability of Forms. An initial supply of NAVMED forms 1448 and 1449 will be provided under separate cover. Additional copies, when required, may be obtained from BUMED (Code 3113).

E. C. KENNEY

Copy to:
CINCLANTFLT
CINCPACFLT
DMOS&RCMOS
FPSO
NATNAVMEDCEN
NAVAVNMEDCEN
NAVMEDADMINU
NDS&RCS
SEAFRONS
NAVMEDRSCHINST
NAVMEDRSCHU 1,2,3,4
NAVMEDFLDRSCHLAB CAMLEJ

Additional copies of this Directive may be obtained from:
Supply Dept., NAVSTA (WASH. NAVYD ANNEX, Code 514.25)
Washington, D. C. 20390

BUMED-713:ml
13 JULY 1964

From: Chief, Bureau of Medicine and Surgery
To: Officer in Charge, Naval Medical Research Laboratory, U. S. Naval Submarine Base, New London, Box 100, Groton, Connecticut, 06342
Officer in Charge, U. S. Naval Medical Neuropsychiatric Research Unit, San Diego, California, 92152
Director, Aerospace Crew Equipment Laboratory, Naval Air Engineering Center, U. S. Naval Base, Philadelphia, Pennsylvania, 19112
Director, Aviation Medical Acceleration Laboratory, Johnsville, Pennsylvania, 18974
Scientific Director, U. S. Naval Radiological Defense Laboratory, San Francisco, California, 94135
Officer in Charge, U. S. Naval Biological Laboratory, Naval Supply Center, Oakland, California, 94614

Subj: BUMED INSTRUCTION 6710.49, "Investigational drugs; guidelines for handling"

Encl: (1) Subj BUMED INST.

1. Addressees of this letter are advised that the subject Instruction, forwarded as enclosure (1) hereto, is to be placed in effect in the above laboratories.

2. Addressees were omitted from distribution of the subject Instruction, but will be included in any future revisions.

W. WILLIAM
Assistant Chief for Research and Military Medical Specialties

Blind Copy to:
Code 456, BUMED

7-20-64 (equipment)
Code 456 action:
Placed in case file with 6710.49 so that it will be flagged for next revision.
Copy sent to Code 3113 for information.

X

UNITED STATES GOVERNMENT

Memorandum

ADMINISTRATIVE CONFIDENTIAL

TO : Director, NIH
THROUGH: Acting Chief, DRFR

DATE: NOV 4 1971

FROM : Associate Chief for Program Development, DRFR

SUBJECT: Progress Report on Survey of Moral and Ethical Aspects of Clinical Investigation

Last winter, discussions of the above subject were initiated in Staff Meetings of the Surgeon General and continued by the Director of NIH. These discussions were extended to meetings of the Institute Directors, NIH, and in a preliminary way to a few of the National Advisory Councils. Orientation conferences were held with the Director, NIH, and his immediate staff for the purpose of assigning responsibility for this survey to DRFR with staff assistance from OPP. A library search was undertaken by the National Library of Medicine to identify existing formal ethical codes for the conduct of clinical research and to collect significant articles dealing with comparative national medical, legal, and legislative positions. In July, an informal, confidential, ad hoc meeting was held with a small group of advisors to the NIH who are knowledgeable about problems relating to clinical investigation and who have had experience in a variety of research institutions and professional societies.

The following represents a summary of the present status of considerations given to this subject, together with a few questions appropriate for early discussion with the Director, NIH, and his staff.

Background Matters of Fact

1. The NIH is deeply involved in support of clinical research. The Institutes presently support between 1,500 and 2,000 research projects which, by their titles, indicate presumptive experimentation involving man. There are about 1,500 clinical research beds supported by grants through the categorical Institutes and DRFR, in addition to 500 beds in the Clinical Center. The NIH has engaged in intramural studies involving more than 1,000 prisoner volunteers and 2,000 normal subject volunteers. Additional NIH involvements in research on man include the Addiction Research Center at Lexington, contract-supported drug screening programs, intramural field studies, and others. The scope of clinical research supported and number of institutions in which clinical research is supported appear to be rapidly increasing.

2. Historically progressive changes in the kinds of clinical research possible to undertake are changing the nature of risks and values relating to clinical research. These changes emerge as a result of growth of techniques permitting operative, physiological, and chemical manipulation of man. Perforce of remarkable advances in the techniques of anesthesia, surgery, biochemical separation and synthesis, immunochemistry and tissue and organ preservation, it has become feasible to undertake increasingly complicated research procedures. At the same time, the range of challenging conceptual advances which can be approached through such clinical research is also rapidly increasing. Accompanying this expansion of research frontiers are unprecedented moral and ethical problems such as those associated with organ donation by normal volunteers.

3. There is no generally accepted professional code relating to the conduct of clinical research. There exist a number of codes which have been drafted on the basis of different assumptions; none of these is entirely satisfactory, nor is any generally accepted in practice. There is a wide range of opinions among professional and lay groups as to what constitutes appropriate professional conduct. These differences apply to questions concerning the balance between individual risks and general social values; the borderline between what is accepted medical practice but actually is experimental in nature and what is conceived to be an outright research venture; what constitutes adequately informed consent, and what values may attach to continuing but perhaps drastically altered conditions of life.

4. The legal status of clinical research is ambiguous. The relationship between the physician and his patient or subject is considered a contractual one, having traditional expectations and restrictions affecting the behavior of each in relation to the other. A change in nature of these relationships and the underlying intentions which obtains during engagement in clinical research is apparently not recognized. The courting of risk without explicit intent of diagnostic or therapeutic benefit is apparently not recognized in our present legal framework. Potential benefits accruing from the virtues of individual contributions to the general good are apparently not recognized. Lawsuits stemming from any untoward outcome of a research endeavor would presumably have to be based on finding fault--that is, on the concept of malpractice. Benefits to the damaged party would presumably have to be based on finding individuals or institutions guilty of malpractice. There is some evidence that lawyers and judges may be giving increased recognition to the legitimacy of clinical research and the possibility

of damage without fault, but these areas in general are as unclear as they are untested.*

5. The NIH supports clinical research in a wide variety of research institutions and hospitals. These institutions and hospitals exhibit an extended spectrum of institutional attitudes and practices relating to the moral and ethical aspects of clinical investigation. There exist conspicuous differences in institutional attitudes toward acceptable professional conduct of clinical research, toward the recruitment and retention of staffs engaged in clinical research, and toward the review of research protocols and the evaluation of results of clinical research carried out on patients and on normal subjects. There is, for example, no uniformity of experience relating to local advisory committee activities respecting the clinical research programs wholly supported by the NIH.

Background Matters of Professional and Social Pressure

1. As the number of investigators, subjects, and institutions engaged in clinical research increases and as the nature of the risks ventured changes according to the extension of research into new areas, a mounting concern is expressed over the possible repercussions of untoward events which are increasingly likely to occur and which may occur in an unfavorable pattern of context. Highly consequential risks are being taken by individuals and institutions as well as the NIH as a direct result of the complexity and ambiguity associated with research on man. The reputation and public confidence respecting individuals, institutions, and the NIH alike could well be rudely shaken by events that are impossible to prevent and by unseemly practices impossible to control. The national health research program could be affected adversely quite inadvertently either in a general way or in respect to the participation of certain indispensable volunteer groups. Social and political pressures such as have been applied in respect to experimentation on animals have never been exerted in the area of clinical research. Yet such pressure could materialize and might vastly affect future medical studies. This burdened atmosphere may contribute to a tendency to reticence, except in quite general terms, concerning the medical research risks and values involved. These issues are so complicated that experts despair of

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* For an analysis of the legal aspects of clinical investigation, see Ladimer, I.: "Ethical and legal aspects of medical research on human beings," reprinted in Ladimer and Newman (ed.), Clinical Investigation in Medicine: Legal, Ethical, and Moral Aspects, Boston University Law-Medicine Research Institute, Boston, 1963, pp. 179-223.

achieving a broad public understanding. Their hope seems to lie instead on conducting clinical research in a professionally responsible manner and hoping to safeguard public confidence in individuals, institutions, and the [illegible] through a favorable "public image."

2. Since World War II, there has been a continuing and conspicuous public interest and enthusiasm for advancing medical research. The public is superficially knowledgeable about advances in clinical research techniques. The lay press is devoting considerable attention to the moral and ethical questions posed by clinical research. For example, very wide publicity has been given in recent months to the experiments at the Jewish Chronic Diseases Hospital, Brooklyn, New York, which resulted in charges of unethical conduct against Dr. Southam of the Sloan-Kettering Institute. This incident and subsequent court cases arising from it have been given extensive coverage in the press. The successes and failures in the field of organ transplantation have also aroused great interest in the ethics of clinical investigation.

3. Professional concerns have been expressed in the form of letters to editors of medical journals and special articles and editorials. A few symposia have been held. There have been a number of individual professional declarations and a few resolutions by professional groups. In June 1964, the World Medical Association issued a declaration of principles governing clinical research. What has appeared in the open literature may reflect no more than the visible parts of an iceberg in comparison with the total professional preoccupation with the moral and ethical aspects of clinical investigation. The British Medical Research Council recently submitted that:

> The progress of medical knowledge has depended, and will continue to depend, in no small measure, upon the confidence which the public has in those who carry out investigations on human subjects, be these healthy or sick. Only in so far as it is known that such investigations are submitted to the highest ethical scrutiny and self-discipline will this confidence be maintained. Mistaken, or misunderstood, investigations could do incalculable harm to medical progress. It is our collective duty as a profession to see that this does not happen and so to continue to deserve the confidence that we now enjoy. (p. 25)*

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* Responsibility in investigations on human subjects, statement by the Medical Research Council (pp. 21-25) in: British Medical Research Council Report for the year 1962-1963.

CONSIDERATIONS RELATING TO NIH GRANTS PROGRAMS

Present Grants Practices

At present, the NIH treats Applications, requests for Supplements, and Progress Reports relating to grants for clinical research the same as for other research. The relatively high national tenor of concern for the moral and ethical aspects of clinical research is reflected in the fact that many clinical investigators, without formal requirements for such information, generally submit comprehensive clinical research protocols. They may describe the mechanisms for local review, conditions for selection of patients and subjects, local practices concerning the provision of informed consent, and other matters relating to professional ethical considerations. Grantees may request support for malpractice insurance. Study Section members, site visitors, and Council reviewers by their own and staff initiative often deliberate ethical questions in relation to grants and may take such deliberations into account in making formal recommendations. There is little attempt to develop consensus as to what clinical research practices should be, or even to define what is the nature of the ethical issues at stake.

Physician-Investigator Practices

There are no adequate data on existing physician-investigator practices relating to patients or normal subject volunteers in respect to the ethical aspects of clinical investigation. There is no generally recognized American ethos, nor any assembled information as to how physicians are educated and indoctrinated during their years of formal and informal preparation for responsibility in clinical research. Professional practices seem to be guided by extension of the principles of very general cultural ethics which are so uniformly accepted they are practically invisible--not even much articulated. It is generally assumed that Americans are less willing than other cultures to encourage individuals or to permit them to suffer risks in a medical setting in relation to any remote or general social benefits. In other areas of social life such sacrifice may be encouraged to the point of conspicuous social pressure. There seems to be a generally accepted professional medical ethos (generally uncodified) that assumes for both medical practice and research that the physician-investigator reduces the risk to his patient, to himself, and to his institution if he shares responsibility for what is done and what is not done with other competent professionals. Therapeutic abortion, sterilization, and amputating surgery are examples of medical procedures which have legal, religious, and cultural ramifications and where shared responsibility is usually required. It is further understood that his individual professional risk is immensely increased if ever the physician-investigator should depart from the considered views of his peers.

Variations in Institutional Practices

The NIH is engaged in supporting research in a wide variety of research institutions and hospitals. In some there is an organizationally distributed responsibility as, e.g., among clinical departments in a hospital associated with a medical school. The usual practice in these cases is that clinical research carried out under the aegis of a particular department is undertaken with the tacit if not formal approval of the department chairman or a responsible professional group within the department, under guidelines for which responsibility is assumed by a clinical research committee, hospital administrator, or dean. In Federal hospitals, such as Veterans Administration Hospitals, such responsibility is focussed on one individual who may operate with the benefit of general guidelines from a local "Dean's Committee" or some other advisory group. Private research institutions and private hospitals may have equally focussed responsibilities for clinical research, but in some instances at least responsibility is distributed among individuals as "equals." The tone of administrative practice within other research centers such as community hospitals is likely to be even less well defined. Actually there does not appear to be any systematic comparative data on institutional practices relating to clinical research.

Problem of Central Control of Clinical Research Practices

1. Ethics of inhibiting the pursuit of research on man. It is evident that medicine does not yet have satisfactory explanations for the cause, cure, and prevention of more than a very few of the simplest diseases and disorders. The cost in human anguish and economic resources of discomfort, disability, and death which is directly attributable to medical ignorance is colossal. That which might be prevented by more insightful, energetic, and creative clinical research is, of course, an unknown quantity but probably of appreciable magnitude. A prime consideration, therefore, relates to the possible inhibition of clinical research which might be effected by almost any form of central control. Group consensus as to what should be permitted, what could be done, and what would be of value may be far less reasonable than the considered view of a single fully qualified investigator. One of our ad hoc committee advisors agreed to the notion of the desirability of the individual investigator sharing responsibility, provided that exclusive and final judgment was not irrevocably retained by the group. The individual investigator in this case would be able to appeal over the objections of his consultative group and be permitted to assume responsibility on his own part alone--letting his career be affected by the outcome of subsequent experience. Other members of the Committee held to the need for fully sharing responsibility.

2. Ethics of employing captive populations. The Nuremberg Code implies prohibition of the use of captive populations such as prisoner volunteers, children in orphan asylums, and likewise strong constraints against the use of coworkers, students, conscientious objectors, and others. The World Medical Association has resolved against the use of captive populations. Some foreign scientists object to the use in this country of prisoner volunteers. It is likely that these objectors do not know the actual conditions of employment of such groups nor the degree of freedom of choice each individual has for his participation. The fact that prisoners do not receive favored treatment or shortened sentences for such contributions is part of the evidence against there being undue persuasion.

3. Ethics of particular clinical research practices. The Chairman of the British Commission on Drug Safety is said to disfavor the use of drugs in normal volunteers and healthy men. The U.S. Drug Amendment Act of 1962 stipulates that animal experimentation should precede the introduction of drugs in man. Errors in both directions, that is, finding toxicities in man when there are none in animals and vice versa, and finding therapeutic benefits in animals when there are none in man and vice versa, are observed even when the drug-testing is carried up to the sub-human primate level. Therefore, man constitutes an indispensable test object for research into drugs that may be therapeutic for man. A judgment that will always remain difficult is how soon and following what kinds of preliminary testing on animals should clinical tests be tried. Outside pressures for the arbitrary limitation of clinical testing in any category could well interfere with needed clinical experience, and yet not actually contribute anything towards improving ethical practices per se.

4. Problems of NIH control. NIH is not in a position to shape the educational foundations of medical ethics, or even the clinical indoctrination of young clinical investigators. More than that, whatever the NIH might do by way of designing a code or stipulating standards for acceptable clinical research would be likely to inhibit, delay, or distort the carrying out of clinical research and to affect grantsmanship more than to influence the actual level of ethical practices. This latter depends, in the last analysis, not on acceptance of and attestation to general principles but on empathic understanding and response to the full implications of one's actions in respect to studying and caring for another human being; the possession of and exercise of wisdom respecting judgments, anticipated and unanticipated, which attach to the conduct of research involving man. These capacities are best instilled by professional precept and cannot be successfully ordained. For a variety of reasons, then, it would be advantageous to the national health research program if any general

guidelines or code of clinical research behavior were developed by a nonfederal body, preferably by a body enjoying the highest professional respect. It is now and will continue to be a positive advantage to the NIH that there are other organizations, Federal and nonfederal, actively engaged in the support of clinical research. In our view, it would add to existing insecurities if the NIH were to assume an exclusive or authoritarian position concerning the definition of ethical boundaries or conditions mandatory for clinical research.

The Ad Hoc Committee made a specific recommendation for changes in NIH practice respecting research grants (and presumably contracts) involving human subjects. See below, item 4, under Summary of Ad Hoc Committee Recommendations.

5. What position for NIH in crisis involving clinical research ethics? In event of strong professional or public reaction to a breach or presumed breach in medical ethics in the conduct of research supported by the NIH, no one doubts that NIH will bear at least professional moral responsibility wherever NIH support is involved. In event of such a crisis implicating the NIH, the tough questions will be:

> Did the NIH give appropriate consideration to the variables in this program involving subjects of research, responsible clinical investigators, institutional policies, practices, and practical safeguards in relation to the risks involved in that particular clinical research?
>
> Was the presumptive risk worth the presumptive gain?
>
> Was preliminary research appropriately advanced prior to its application to man?
>
> Did the review and approval practices arrive at a professionally justifiable position?
>
> What did the NIH do prior to the occurrence of the untoward event that served to preclude any such event taking place and to assure appropriate resuscitative and rehabilitative practices once the event took place?
>
> If NIH practices were negligent in this instance, what about its practices elsewhere?
>
> Was the NIH invited and did the NIH contribute adequately through its advisory mechanisms to secure the benefits of foresight and wisdom relating to the potential risks being ventured in this instance?

What has the NIH done specifically to protect the interests and well-being of subjects, investigators, and institutions, as well as the national health research program, through studies and devices, including possibly new social instruments, for the assurance of protection of all parties concerned in event of untoward occurrence, without the requirement that fault be established?

What specifically has the NIH done to secure improved practices in respect to informed consent?

What has the NIH done, in general, to illuminate and to foster professional understanding of the moral and ethical aspects of clinical research?

What has the NIH done toward the formulation, communication, and maintenance of suitable ethical standards for clinical investigation?

What has the NIH done, in general, to explore the nature of moral and ethical aspects of clinical research as these extend into areas of religion, law, and philosophy?

In the light of such considerations, the Ad Hoc Committee made four recommendations:

SUMMARY OF AD HOC COMMITTEE RECOMMENDATIONS
June 14 - 15, 1964

1. That an appropriate professional group be encouraged to formulate a statement of principles relating to moral and ethical aspects of clinical investigation which could be appropriate for guidance of the medical research community.

The principles should be sufficiently general to be reasonably enduring, yet explicit enough to deal with genuine issues. If the statement is well founded, it will illuminate the positive gains for which clinical investigation is indispensable and it will serve as a source of inspiration and guidance for clinical investigators, research institutions, and supporting agencies.

Among the professional groups which might be suitable for this undertaking are the American College of Surgeons, the American College of Physicians, the American Society of Clinical Investigators, and the Association of American Physicians. Perhaps two or more of these groups could be drawn together appropriately for this national purpose through the National Academy of Sciences. It was unanimously agreed that the statement should be formulated in the spirit of professional conscience and self-determination rather than in the spirit of Federal control by the NIH or PHS.

2. That in order to provide a more solid foundation for future determination of the risk - the ethical responsibilities involved in clinical research trials - there is a need for factual information concerning the role and potential of medical experiences in the prevention of illness, saving of lives, and other medical, social, and economic values obtained through the voluntary element of risks and acceptance, however unknowingly, of certain losses.

Such a study, aimed at providing specific information, confidential when necessary, could draw in part on the experiences of the categorical and General Clinical Research Centers supported by the NIH, and the Clinical Center, including an appraisal of the experiences of local review committees and the operational experiences relating these committees and the investigators engaged in the actual research activities.

3. That the NIH should consider providing consultative advice, at the request of grantees, concerning ethical problems and risk minimizing practices that might be appropriate for the furtherance of clinical research.

When faced with a difficult problem involving the moral and ethical aspects of clinical investigation, an investigator or grantee institution would be enabled to request NIH assistance in securing expert advice and consultation from among individuals having competence and experience relevant to the particular problem. Such assistance would enable the investigator and institution to benefit from broader experiences and more specific competences than might be available locally. The practice would automatically contribute to the extension and improvement of clinical research practices and to the dissemination of improved insight into these problems on a national scale.

4. That because of the special nature of research projects involving human subjects, research grant documentation relating to clinical investigation should be identified for special consideration throughout the NIH-PHS review process.

Grant applications, renewals, supplements, and progress reports dealing with clinical studies should contain specific information, where appropriate, as to the ethical considerations involved in the selection and participation of human subjects, local practices regarding informed consent, and local review and guidance mechanisms relating to clinical studies. These documents should also describe, where appropriate, how changes in the course of the research involving the use of human subjects will be reviewed locally. This type of information could assist NIH staff and review groups in becoming acquainted with and giving due and

disproportionate consideration to ethical problems not with in these research areas. These considerations could contribute appropriately to the review group's assessment of (i) the competence of the investigator to undertake the study, and (ii) the adequacy of the institutional setting in which the research is conducted. Project site visits should ordinarily be the rule where legitimate doubt exists concerning ethical considerations. The Ad Hoc Committee also emphasized that all evaluations by reviewing groups raising questions about moral and ethical aspects of clinical research projects should be explicit and sufficiently detailed as to what exactly is the ethical question at stake and what may be the nature of the aversion or doubt.

Respectfully submitted,

Robert B. Livingston, M.D.

ARMY REGULATION
No. 40–7

HEADQUARTERS
DEPARTMENT OF THE ARMY
WASHINGTON, DC., *15 November 1964*

MEDICAL SERVICE

CLINICAL USE OF INVESTIGATIONAL DRUGS

1. **Purpose and scope.** This regulation prescribes the policies and procedures applicable to all clinical use of investigational drugs under the auspices of the Department of the Army.

2. **Definitions.** For the purpose of this regulation, the following definitions apply:

a. Drug. Any substance intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man; and any substance (other than food) intended to affect the structure or any function of the human body.

b. Investigational drug. A new drug, not yet approved by the Commissioner of Food and Drugs, Department of Health, Education, and Welfare (hereinafter referred to as FDA) for general use by the public as a safe and efficacious drug, and that is proposed for clinical study under Department of the Army auspices after adequate preclinical information has been obtained.

c. Clinical use. The administration of a drug to man.

3. **Procedure to be followed.** *a. Approval.* The clinical use of an investigational drug may be authorized only upon written approval of The Surgeon General (see also par. 7*b*). Each investigator who requests authority to conduct or is officially requested to conduct either the clinical pharmacology or clinical trials of an investigational drug will submit a signed completed application and three copies, indorsed by the hospital or other medical facility commander, to The Surgeon General, ATTN: Chairman, Army Investigational Drug Review Board (AIDRB), Department of the Army, Washington, D.C., 20315, using the following format:

Investigator's Statement

I. Background data.
- A. Name of investigator.
- B. Date of request.
- C. Name or other clear identification of drug.
- D. Name of manufacturer or other source of drug.
- E. Qualifications of investigator in detail or by reference to details already on file in Army records.
- F. Name and address of facility or facilities where investigations will be conducted.
- G. All known relevant information about past use or pertinent reference thereto available to both the investigator and the drug supplier, including all preclinical data, and all other information justifying the clinical investigation (i.e., the safety and rationale of the proposed study).

*This regulation supersedes paragraph 735, AR 40–2, 4 November 1960.

TAGO 677A—Nov. 750–469*—64

Incl 14 to Incl 12
to Tab B

II. Plan and Conduct of Proposed Clinical Investigation.
- A. Specific purpose and military need for or urgency of proposed clinical investigation.
- B. Approximate number of subjects, their age, sex, condition, and other pertinent information relevant to the conditions of the investigation.
- C. Number of subjects to be employed as controls (if any) and some information as in B above for such controls.
- D. An outline of the phases of the investigation already planned either in detail or by reference to details already on file in Army records. This outline may include reasonable alternates and variations, and will be supplemented or amended when any significant change in direction or scope of the investigation is undertaken.
- E. Description or copies of forms used to record data.

b. Review and evaluation. The AIDRB will review and evaluate all proposals received, enter into any indicated correspondence with the investigator, and, to the extent that the proposal is rejected in whole or in part, will transmit same to the investigator. To the extent that the AIDRB approves a proposal, it will transmit its recommendation to The Surgeon General, who will then confirm or disaffirm in whole or in part the Board's approval of the proposal in question.

c. Bases for disapproving proposals for investigational drug—studies. Either the AIDRB or The Surgeon General may withhold approval to study an investigational drug clinically if it is determined—

(1) That there is substantial evidence to show the drug to be too dangerous for use for the purposes and in the manner for which it is proposed for investigational use.

(2) That the manufacturing methods are inadequate to maintain appropriate standards of quality needed to assure safety and give significance to the clinical investigation of the drug.

(3) That the overall plan for clinical investigation does not appear reasonable or otherwise worthy of support.

4. Composition of Board (AIDRB). The board will be composed of the Special Assistant to The Surgeon General for Research and Development or his personally selected designee as Chairman, and at least four other professionally qualified individuals designated by The Surgeon General, all of whom will serve at The Surgeon General's pleasure, and one of whom will be designated as the Recorder.

5. Record-keeping requirements. *a. By investigator.* Each investigator subject to this regulation will maintain a record of clinical investigation separate from the patient's clinical record. This record of clinical investigation will include, minimally, a list of patients receiving the investigational drug; the name, lot number, date and quantity of investigational drug prescribed; case histories; the details of clinical observations, tests, and laboratory procedures carried out on each subject before, during, and after administration of the drug in question.

b. By custodian. A complete record of each investigational drug will be maintained by an official designated by the commanding officer of the medical unit or installation, normally the pharmacy officer, if the investigational drug is being used in an Army facility, and by the investigator himself, or a responsible individual designated by him for the purpose, when the drug is being used under a Department of the Army contract or grant. This record will include the following information:

(1) Name of drug.
(2) Manufacturer, or other source of drug.
(3) Amount and date received.
(4) Expiration date, if any.
(5) Lot or control number.
(6) Date of authority to use.
(7) Names of individuals authorized to prescribe the drug.
(8) Name of prescribing physician or dentist.
(9) Date on which use of the drug is terminated, if applicable.
(10) Date on which use of the drug is approved for general use as a safe and efficacious drug, if during course of investigation.

c. Retention period. All records required by this paragraph will be kept 3 years after completion of the project and then retired permanently. See AR 345-210, File No. 903-38.

6. Reporting requirements. Progress reports will be submitted to The Surgeon General, ATTN: Chairman, AIDRB, by the responsible investigator at least once annually. A final report will also be submitted by the investigator to the Army Investigational Drug Review Board promptly on termination of the investigation. In addition, unusual or important observations will be reported promptly to such Board, particularly if they involve any adverse effect that may be regarded as caused by the new drug; if the adverse effect is alarming, it will be reported to such Board immediately.

7. Special conditions applicable to clinical investigations of new drugs. *a.* The investigator will make certain that the investigational drug is administered to subjects only under his personal supervision or under the supervision of other qualified personnel to whom he has delegated this authority.

b. The investigator will make certain that all subjects participating in the investigation or their representatives are fully informed and understand that the new drug is being used for investigational purposes. He will obtain the written consent of the subjects, or their representatives, except where this is not feasible, or, in the investigator's professional judgment, is contrary to the best interests of the subjects. When the purpose of administering an investigational drug is not to benefit the individual to whom it is administered, final approval for the use of volunteer subjects will be obtained as provided in paragraph 6, AR 70–25. Benefit to the individual is defined as the administration of a drug to an individual expected to result in the diagnosis, mitigation, treatment, cure, or prevention of disease or injury of the same individual.

8. Information to be furnished FDA. The Surgeon General will furnish information copies of the following to authorized representatives of FDA, provided personnel security clearances, if needed, are obtained:

a. Alarming and other adverse reports to The Surgeon General on the effects of an investigational drug when received.

b. Any existing Department of the Army report concerning an investigational drug specifically requested by an authorized representative of FDA.

c. In the case of unclassified clinical studies of investigational drugs, The Surgeon General will transmit copies of the "Investigator's Statement," signed copies of the AIDRB's and The Surgeon General's evaluation and approvals to the Commissioner of Food and Drugs, Department of Health, Education, and Welfare, Washington, D.C., 20203. In the case of classified clinical investigations of new drugs, and in the case where the investigational drug to be studied is being sponsored by the pharmaceutical industry, such materials need not be transmitted to FDA, subject to the provisions of *a* and *b* above, but Form FD 1571 (see 28 Federal Register 179), FDA's usual claim for exemption, will be forwarded to The Surgeon General for transmittal to FDA after approval by The Surgeon General.

d. Nothing herein should be construed as precluding The Surgeon General or his delegate from transmitting any Department of the Army information pertaining to investigational drugs which, in their discretion, appears should be of interest to FDA.

9. Medical emergencies. In crucial situations The Surgeon General, ATTN: MEDPS-CM, may approve short term use of an investigational drug being sponsored by a pharmaceutical firm on an individual patient, without submission of the Investigator's Statement prescribed in paragraph 3, upon a hospital commander's request for same. Such request will include the following information minimally: patient's name, diagnosis, name and quantity of the drug proposed for use, medical officer responsible for the patient, and nature of the medical emergency. In cases where The Surgeon General approves emergency use of an investigational drug being sponsored by a pharmaceutical firm, the responsible investigator will furnish both a completed FD 1573 (Statement of Investigator (see 28 Federal Register 179)) to the sponsoring pharmaceutical firm and a signed copy of said Form FD 1573 to The Surgeon General as expeditiously as circumstances permit.

10. Custody and dispensing of investigational drugs. Investigational drugs in the custody of the Department of the Army will be stored and dispensed in accordance with the applicable provisions of AR 40–2, subject to the provisions of paragraph 5 above.

11. Army contracts. All contracts under which investigational drugs are to be clinically investigated will contain the following clause:

AR 40-7

CLINICAL STUDY OF INVESTIGATIONAL DRUGS

a. The Contractor agrees that before undertaking to conduct either the clinical pharmacology or clinical trials of an investigational drug under a Department of the Army contract, it will submit for the written approval of The Surgeon General, Department of the Army, a signed completed application and three copies to The Surgeon General, ATTN: Chairman, Army Investigational Drug Review Board, Department of the Army, Washington, D.C. 20315, using the following format:

Investigator's statement

I. Background data.
- A. Name of investigator.
- B. Date of request.
- C. Name or other clear identification of drug.
- D. Name of manufacturer or other source of drug.
- E. Qualifications of investigator in detail or by reference to details already on file in Army records.
- F. Name and address of facility or facilities where investigations will be conducted.
- G. All known relevant information about past use or pertinent reference thereto available to both the investigator and the drug supplier, including all preclinical data, and all other information justifying the clinical investigation (i.e., the safety and rationale of the proposed study).

II. Plan and Conduct of Proposed Clinical Investigation.
- A. Specific purpose and military need for or urgency of proposed clinical investigation.
- B. Approximate number of subjects, their age, sex, condition and other pertinent information relevant to the conditions of the investigation.
- C. Number of subjects to be employed as controls (if any) and same information as in B above for such controls.
- D. An outline of the phases of the investigation already planned either in detail or by reference to details already on file in Army records. This outline may include reasonable alternates and variations, and will be supplemented or amended when any significant change in direction or scope of the investigation is undertaken.
- E. Description or copies of forms used to record data.

b. The Contractor agrees that each of its investigators who conduct either the clinical pharmacology or clinical trials of an investigational drug will maintain a record of clinical investigation separate from the patient's clinical record. This record of clinical investigation will include, minimally, a list of patients receiving the investigational drug; the name, lot number, date, and quantity of investigational drug prescribed; case histories; the details of clinical observations, tests, and laboratory procedures carried out on each subject before, during, and after administration of the drug in question.

c. The Contractor agrees also that either its responsible investigator or a responsible individual designated by him for the purpose will maintain a complete record of each investigational drug used under a DA contract for at least 3 years after completion of the investigational drug study. This record will include the following information:

1. Name of drug.
2. Manufacturer, or other source of drug.
3. Amount and date received.
4. Expiration date, if any.
5. Lot or control number.
6. Date of authority to use.
7. Names of individuals authorized to prescribe the drug.
8. Names of prescribing physician or dentist.
9. Date on which use of the drug is terminated, if applicable.
10. Date on which use of the drug was approved for general use as a safe and efficacious drug, if during course of investigation.

d. The Contractor agrees to submit progress reports to The Surgeon General, ATTN: Chairman, AIDRB, at least one annually, and to submit a final report on termination of the investigation. In addition Contractor agrees to promptly report to the AIDRB any unusual or important observations occurring during the course of the investigational drug study,

TAGO 6771A

particularly if they involve any adverse effect that may be regarded as caused by the new drug; if the adverse effect is alarming, it will be reported to the AIDRB immediately.

e. Special Conditions Applicable to Clinical Investigation of New Drugs: The Contractor agrees to make certain that the investigational drug is administered to subjects only under the personal supervision of the responsible investigator or a qualified person to whom the responsible investigator has delegated this authority. The Contractor also agrees to make certain that all subjects participating in the investigation or their representatives are fully informed and understand that the new drug is being used for investigational purposes. The written consent of the subjects, or their representatives will be obtained except where this is not feasible or, in the responsible investigator's professional judgment, is contrary to the best interests of the subject. When the purpose of administering an investigational drug is not to benefit the individual to whom it is administered, final approval for the use of volunteer subjects will be obtained as provided in paragraph 6, AR 70-25. Benefit to the individual is defined as the administration of a drug to an individual expected to result in the diagnosis, mitigation, treatment, cure, or prevention of disease or injury of the same individual.

12. Army grants. All Department of the Army grants under which investigational drugs are to be clinically investigated will contain clauses requiring the grantee to comply with the requirements of paragraphs 3, 5, 6, and 7.

[MEDJA]

By Order of the Secretary of the Army:

HAROLD K. JOHNSON,
General, United States Army,
Chief of Staff.

Official:
J. C. LAMBERT,
Major General, United States Army,
The Adjutant General.

Distribution:
Active Army: To be distributed in accordance with DA Form 12-9 requirements for Medical Services—D.
NG: None.
USAR: None.

U.S. GOVERNMENT PRINTING OFFICE: 1966

NAVAL MEDICAL RESEARCH INSTITUTE
NATIONAL NAVAL MEDICAL CENTER
BETHESDA XX MARYLAND 20014

NMRI-013-mh
1070/4-2
Ser: 3986
30 November 1964

From: Commanding Officer, Naval Medical Research Institute, National Naval Medical Center, Bethesda, Maryland 20014
To: Secretary of the Navy
Via: (1) Commanding Officer, National Naval Medical Center, Bethesda, Maryland 20014
(2) Chief, Bureau of Medicine and Surgery
(3) Chief of Naval Personnel

Subj: Authorization to use human volunteers as subjects for study of effects of hypoxia on the visual field; request for

Ref: (a) MANMED, Article 1-11
(b) BUPERS ltr. Pers-A212c-11g of 27 October 1964

1. In accordance with reference (a), it is requested that permission be granted to utilize human volunteers as subjects in a study of the effects of hypoxia on the visual fields in humans. Subject study pertains to Bureau of Medicine and Surgery Research Subtask MR 005.13-4001.06 "Effect of Gradient Pressures upon Physiological Systems" and is a new phase unde that subtask. The objective is to confirm or define more exactly effects of hypoxia which have been reported but not adequately investigated under controlled conditions. Reference (b) authorized five (5) enlisted billet for duty as experimental test subjects in high altitude, space and underwater research.

2. A hemispheric bowl perimeter and attendant techniques have been developed which are directly applicable to human subjects. Experience indicates that the oxygen deprivation levels to be used cause no harmful after-effects, although momentary discomfort may occur during actual exposure.

3. As a part of the study of behavioral performance and over-all visual acuity and pattern detection, the following area is specifically proposed for investigation:

a. The psycho-physiological effects of varying degrees of hypoxia on the size of the visual fields in human subjects.

BUMED-71:ml
6500
4 DEC 1964

SECOND ENDORSEMENT on CO NMRI ltr NMRI-013-mh 1070/4-2 Ser 3986 of 30 Nov 1964

From: Chief, Bureau of Medicine and Surgery
To: Secretary of the Navy
Via: Chief of Naval Personnel

Subj: Authorization to use human volunteers as subjects for study of effects of hypoxia on the visual field; forwarding of

1. Forwarded, recommending approval.

2. All subjects in these studies will be volunteers.

3. It is not considered that these procedures will impose any undue hazards on the health or life of the volunteers involved.

R. B. BROWN
Acting

Copy to:
CO, NMRI
CO,NNMC

6500 (Human Volunteers), 3900

Pers-A212c-llg
10 DEC 1964

THIRD ENDORSEMENT on CO, NMRI ltr NMRI-013-mh 1070/4-2 Ser 3986 of 30 Nov 1964

From: Chief of Naval Personnel
To: Secretary of the Navy

Subj: Authorization to use human volunteers as subjects for study of effects of hypoxia on the visual field; forwarding of

1. Forwarded, recommending approval.

Leon I. Smith Jr.

LEON I. SMITH, JR.
BY DIRECTION

Copy to:
CO, NMRI
CO, NNMC
BUMED

Copy Com
Bu Pers

18 DEC 1964
Approved _____ 19__

PAUL B. FAY, Jr.
Under Secretary of the Navy

OFFICIAL

RETURNED TO ORIGINATOR FOR
DISPOSITION THIS DATE 12/21/ 5
G.A.

OFFICIAL

NMRI-013-mh
1070/4-2

4. A medical officer, qualified in Aviation Medicine, will be available at all times during experimentation. The facilities of the National Naval Medical Center are readily available for consultation or medical emergencies.

5. It is proposed to use ten (10) volunteers at convenient times during a six months' period. Subject volunteers are male, active duty personnel affiliated with the Physiological Sciences Department of the Naval Medical Research Institute who are then currently receiving incentive pay. Subjects will be exposed to varying partial pressures of oxygen corresponding to different levels of altitude. A medical file will be maintained for each subject. The file will include a Standard Form 88 (Report of Physical Examination), a Standard Form 89 (Report of Medical History), a signed Consent to Voluntarily Participate in Research Experiment (NMRI Form 3)1 a Chronological Record of Medical Care (Standard Form 600), and other such tests considered necessary by the attending medical officer before, during, and after the periods of exposure.

JOHN R. SEAL

A GUIDE FOR THE PREPARATION OF APPLICATIONS FOR THE MEDICAL USE OF RADIOISOTOPES

November 1965

DIVISION OF MATERIALS LICENSING
U.S. ATOMIC ENERGY COMMISSION
WASHINGTON, D.C. 20545

For sale by the Superintendent of Documents, U.S. Government Printing Office
Washington, D.C., 20402 - Price 45 cents

PREFACE

The Atomic Energy Act of 1954, as amended, charges the United States Atomic Energy Commission with, among other things, responsibility for regulating the receipt, possession, and use of byproduct material. The Commission is authorized to establish by rule, regulation, or order, such standards, instructions and procedures to govern the possession and use of byproduct material as it may deem necessary or desirable to protect health or to minimize danger to life or property.

In the performance of its regulatory functions, the Commission has promulgated the regulations contained in Title 10 of the Code of Federal Regulations. The following regulations are included in Title 10 and are particularly pertinent to the subject of this guide:

1. Part 20, "Standards for Protection Against Radiation" (10 CFR 20).
2. Part 30, "Rules of General Applicability to Licensing of Byproduct Material" (10 CFR 30).
3. Part 35, "Human Uses of Byproduct Material" (10 CFR 35).

Current copies of Commission regulations may be obtained from the Division of Materials Licensing, U.S. Atomic Energy Commission, Washington, D.C., 20545, or from any of the following U.S. Atomic Energy Commission Regional Compliance Offices:

Director, Region I
Division of Compliance, USAEC
376 Hudson Street
New York, N.Y. 10014

Director, Region II
Division of Compliance, USAEC
50 Seventh Street, Northeast
Atlanta, Ga. 30323

Director, Region III
Division of Compliance, USAEC
Oakbrook Professional Building
Oak Brook, Ill. 60523

Director, Region IV
Division of Compliance, USAEC
10395 W. Colfax Avenue
Denver, Colo. 80215

Director, Region V
Division of Compliance, USAEC
2111 Bancroft Way
Berkeley, Calif. 94704

This guide describes the kinds of information to be submitted in applications for the possession and use of radiopharmaceuticals. Its use should result in the submission of more complete applications. The Commission will request additional information if necessary in order to provide reasonable assurance that the applicant has established an adequate radiation safety program. (See Sec. 30.32(b) of 10 CFR 30.) Requests for additional information delay final action on the application and may be avoided by a thorough study of Commission regulations and this guide prior to filing the application.

This guide is intended only for general information and should not be considered a substitute for the applicant's careful evaluation of the proposed use of byproduct material or for assuring that the application correctly and adequately describes the radiation safeguards and procedures to be followed.

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APPENDICES

APPENDIX F

NON-ROUTINE MEDICAL USES OF BYPRODUCT MATERIAL

Experimental and nonroutine medical uses of byproduct materials include all human uses not specified in appendix D. Such uses may be classified into one of two phases of development:

Clinical Research applies to a new use of byproduct material in humans. Little or nothing is known about the procedure and little or nothing has been published on the subject. The basis for proceeding with the new use in humans is derived from knowledge obtained from animal studies. This phase of development includes the initial introduction into humans and initial trials on a limited number of patients.

Clinical Evaluation applies to the planned testing of a new diagnostic or therapeutic procedure in an appropriate series of control and diseased humans. The procedure and results of clinical research will ordinarily have been reported in the literature or at meetings. If adequate information has not been published, the applicant should have spent sufficient time with those who developed the test, to be thoroughly familiar with the details.

The *clinical research* phase of experimental or nonroutine medical use of byproduct material is normally limited to licensees who have broad experience in the use of radioisotopes and who have appropriate facilities and equipment available to conduct research. Research should be pursued by groups of competent investigators representing different disciplines rather than by single individuals. The individual physician to be designated on the license as the authorized user should normally have broad and varied experience in the use of radioisotopes and in clinical research investigation.

The clinical evaluation phase of experimental or nonroutine medical use of byproduct material is normally limited to licensees under the supervision of an individual physician with broad experience in clinical evaluation and the use of radioisotopes and under the guidance of a radioisotope committee representing a number of disciplines. Adequate resources to conduct the trials shall be available.

Applications for experimental or nonroutine uses of byproduct material in humans are reviewed with the assistance of the Commission's Advisory Committee on the Medical Use of Isotopes. Applications should be supported by a research protocol which includes:

1. Title of study.

2. The purpose for conducting the study. Indicate whether the study is to be clinical research or clinical evaluation and explain why.

3. The plan of investigation in sufficient detail to permit a critical evaluation of the methods for conducting the experiments and the controls established.

4. A statement as to whether any planned complementary drug or radioisotope administration is contemplated in conjunction with the study.

5. A statement about the expected fate of the isotope administered and if the procedure is for therapy, a statement about the expected effects.

6. A. *If the application is for clinical research*, an outline of related work conducted by the applicant or others in laboratory animals and in humans, including data on localization, effective half-life, and radiation dosage. If no work has been conducted in animals, explain why. Pertinent references and a brief abstract prepared by the applicant of published or unpublished material should be submitted. (The brochure of a commercial supplier is not a satisfactory authority for this purpose. It is not necessary to include with the application reprints of references.)

B. *If the application is for clinical evaluation*, pertinent references and a brief abstract prepared by the applicant of published or unpublished material, including information on localization, effective half-life, and radiation dosage. (The brochure of a commercial supplier is not a satisfactory authority for this purpose. It is not necessary to include with the application reprints of references.)

7. A description of the human subjects to be studied:

A. Persons without manifest disease—number, method of selection, age range.

B. Persons with manifest disease—number, nature of pathology, method of selection, age range.

C. Pregnant women shall ordinarily be excluded from any test not involving the condition of pregnancy itself. Specify whether or not pregnant women will be tested and if so, explain why.

8. Confirmation that consent of human subjects, or their representatives, will be obtained to participate in the investigation except where this is not feasible or, in the investigator's professional judgment, is contrary to the best interests of the subjects.

9. The dose range (microcuries or millicuries) to be administered and the method of administration.

10. Calculations of the radiation doses delivered to the whole body and to the critical organ(s). The calculations shall contain information about:

A. The expected half-life in various organs.

B. The relationship between the retained isotope and the permissible body burden for occupational exposure (except for therapy).

C. The rationale for using the dose selected.

D. The radiation dose due to other simultaneous or accompanying radioactive isotope test which may be administered.

11. A statement of the institutional resources available to support the study including:

A. Physical facilities and equipment especially suited for the study under consideration.

B. Availability of clinical material.

C. Types of consultation or collaboration available including the name of the sponsor of the study if other than the applicant.

12. Qualifications of the individual physician who will be responsible for the study, including a summary of research training and experience and pertinent training or experience in the use of radioisotopes.

13. Estimated time needed to complete the study.

14. A schedule for reporting results of the study, and an outline of the type of information to be included in the report. The schedule can be in terms of time intervals or number of subjects studied. If studies are to be long range, interim reports should be provided.

NIH-PHS 14

UNITED STATES GOVERNMENT

Memorandum

TO : Dr. Luther L. Terry
Surgeon General

DATE: September 16, 1965

FROM : Edward J. Rourke
Assistant General Counsel

SUBJECT: Research grants--Clinical--PHS responsibility--Fink v. Jewish Chronic Disease Hospital (New York Supreme Court, Kings County)

Dr. Kenneth Endicott has no doubt already informed you of the demand by the attorney for the defendant hospital in the above case that the Public Health Service, the Sloan-Kettering Institute, the American Cancer Society, and certain physicians take over the defense of this action and indemnify the hospital for any damages it may be required to pay the plaintiff. The plaintiff complains, in brief, that while a patient at the hospital for arthritis, cancer cells were injected under his skin without his knowledge and consent and as part of a research project not related to his treatment. He claims this constitutes a wrongful action and malpractice, contrary to medical standards of the community.

The hospital's attorney expresses the view that such use of the plaintiff was without the approval of the hospital authorities, that it was done by Sloan-Kettering on its own "account" and in furtherance of its own "business", and that the American Cancer Society and the PHS "promoted, supported or caused" this research to be undertaken and should thus stand responsible in lieu of the hospital.

Even though we have furnished Dr. Endicott with a draft letter rejecting this demand as to the PHS, we anticipate that the demand was a preliminary step to efforts to join the PHS and the other agencies as codefendants or as "third party defendants" to which the hospital would look to pay any damages assessed against it. Although we expect to resist these efforts, the situation presents certain matters we think important for policy consideration whatever may be the outcome of this litigation.

The policy considerations may begin with the attention that has been given for some time by Dr. Ernest Allen to amending the PHS research project grant regulations to make expressly clear that the PHS does not supervise or control the conduct of research it supports by grant. The hope is

that by this express clarification of the relationship between grantor and grantee, the Service will have a better basis for denying liability for damages arising from a grantee's conduct of research.

Such a step, however, seems to us not likely to be considered an adequate measure of PHS "responsibility", at least in a general if not a legal sense. Where, as in this context, you have adequate authority to impose grant conditions reasonably related to your public purpose, the question will necessarily arise as to whether you should continue to impose no conditions or exercise no review as to those aspects of supported research that give special concern because it involves the use of human subjects. We think it not unlikely that questions will arise of whether we can continue in this area the traditional avoidance of any implication of Federal "control" of research supported by Federal funds.

A variety of mechanisms might be available. For example, applicants seeking funds for clinical research might be required to furnish an assurance with their application that effective, informed consents will be obtained from all participating subjects and that other principles of general agreement in this area will be adhered to. To include this type of requirement in your regulations would help define what responsibilities you have undertaken and, perhaps of greater value, what responsibilities you have not undertaken.

On the whole, we suggest that the vigorous concern in many quarters as to the use of other animals in research is not likely in the long run to be greater than that for the use of the human animal even if the Service role is only fund support. We suggest that explicit policy formulation here, and its expression in controlling mechanisms such as the regulation, is needed.

AIR FORCE REGULATION
NO. 169-8

DEPARTMENT OF THE AIR FORCE
Washington, 8 October 1965

S/S by AFR 169-8, 27 May 68

Medical Education and Research

USE OF VOLUNTEERS IN AEROSPACE RESEARCH

This regulation establishes the policies and procedures for using human volunteers in aerospace research projects.

1. Application of This Regulation. The provisions of this regulation:

a. *Apply to:*

(1) Research, development, test, and evaluation (RDT&E) procedures that may result in distress, pain, damage to health, physical injury, or death of the subject. Such tests usually are conducted to determine either the level of human tolerance for a condition that may be imposed by Air Force operations or the adequacy of equipment designed for human use (see AFR 80-14).

(2) Investigations of disease, new treatment procedures, and drug research conducted by the USAF Medical Service for the benefit of patients.

b. *Do not apply to:*

(1) Any programs, tasks, and tests that involve inherent occupational hazards to health or exposure to potentially hazardous situations such as those encountered as a part of training or other normal duties, e.g., flight training, jump training, bailout studies, fire drills, gas drills, and handling of explosives.

(2) The human factors research portions of a research project when they involve normal training or other normal military duties and when disclosure of the research conditions would defeat the purpose of the investigation by revealing the artificial nature of the experimental conditions.

2. Voluntary Informed Consent. The voluntary informed consent of the human subject is absolutely essential.

a. The volunteer must have the legal capacity to give his consent and must give it freely.

b. Before a volunteer gives his consent he must be given an adequate explanation of the research study, i.e., its nature, duration, and purpose; the methods and means by which it will be conducted; and any foreseeable inconveniences, hazards, and effects on his health which could result from his participation in the experiment. The volunteer must also be told about any parts of the testing program which cannot be stopped or controlled by either the test subject or the person conducting the test.

c. The consent of the volunteer will be given in writing in the format shown by attachment 1. The volunteer must sign the consent in the presence of at least one witness who will then attest the volunteer's signature by signing in the place provided.

3. Principles, Policies, and Requirements for the Use of Volunteers in Hazardous Aerospace Research:

a. All essential preliminary tests with laboratory animals, dummies, and other human simulators must be conducted and evaluated before a human subject is used. Research on human volunteers will be conducted only to validate important results that are essential to a program.

b. Research studies using human volunteers will be so conducted that all unnecessary physical or mental suffering or injury is avoided. Such studies will not be conducted if there is reason to believe that disabling injury or death will probably occur. To this end, a physician will conduct and record the examinations he feels necessary before the test project begins.

c. The degree of risk to which a volunteer is exposed will never be more than is absolutely essential because of the urgency and importance of the solution of the problem that made the research project necessary.

d. The research project will be conducted by scientifically qualified persons; a physician will be responsible for the medical care of the volunteer. The physician or the principal investigator will have the authority to terminate the research study at any time.

e. The volunteer will be informed that:

(1) At any time during the course of

OPR: AFMSPA
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the research project, he will have the right to revoke his consent and withdraw from the test without prejudice to himself.

(2) The principal investigator or attending physician may terminate the experiment at any time he considers it necessary, regardless of the volunteer's wishes.

4. Approval to Conduct Research Involving Volunteers:

a. *Action by Originating Laboratory.* The commander conducting the research will appoint a research committee composed of three scientists; the chairman must be a physician. Committee members will not include either the principal investigator or the physician responsible for the medical care of the volunteer during the experiment. This committee must review and approve or disapprove all proposed RDT&E protocols that will require use of human volunteers.

b. *Action by the Surgeon General.* No research using volunteers will be undertaken without prior review and clearance by the Surgeon General. This will be accomplished by the submission of DD Forms 1498, "Research and Technology Review," through channels to the Surgeon General (AFMSPA). In no case will a project using human volunteers be initiated unless a DD Form 1498 has been approved by the Surgeon General. For urgent proposals to which DD Forms 1498 are not applicable, the Surgeon General's approval may be granted by telephone with confirmation by letter. Research projects performed under AFR 169-6 that involve human volunteers will be considered approved under the provisions of this regulation when letter approval by the Surgeon General is received. Research under AFR 169-6 need not be delayed pending submission and approval of DD Form 1498.

5. Publications Pertaining to Human Volunteers. All printed papers or articles that pertain to the use of human volunteers will contain the following footnote: "The voluntary informed consent of the subjects used in this research was obtained as required by AFR 169-8."

BY ORDER OF THE SECRETARY OF THE AIR FORCE

J. P. McCONNELL
General, U. S. Air Force
Chief of Staff

OFFICIAL

R. J. PUGH
Colonel, USAF
Director of Administrative Services

Attachment
Format for Volunteer Consent

(FORMAT FOR VOLUNTEER CONSENT)

Facility_____ Date_____

CONSENT OF HUMAN TEST SUBJECT

1. Having been fully advised of the dangerous nature and possible harmful consequences, I hereby volunteer to participate as a human test subject in the following experiment or series of experiments:

_____

(State nature of investigation, test, or experiment)

2. I further acknowledge that my consent has been freely given and that I have been informed that I may withdraw my consent at any time insofar as the nature or stage of the experiment permits.

_____

(Signature of test subject)

_____

(Witness)

P45-5.1 A1

OPTIONAL FORM NO. 10 5010-107
MAY 1962 EDITION
GSA GEN. REG. NO. 27

UNITED STATES GOVERNMENT

Memorandum

TO : Dr. Jack Masur
Director, Clinical Center, NIH

DATE: December 6, 1965

FROM : Executive Secretary, National Advisory Health Council

SUBJECT: Resolution of Council

Attached are two copies of resolution passed by the National Advsiory Health Council at its meeting December 3rd, 1965.

Dr. S. John Reisman
Medical Director

Buy U.S. Savings Bonds Regularly on the Payroll Savings Plan

PHS-NIH 23

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
WASHINGTON, D.C. 20201

REFER TO:

February 8, 1966

TO : The Heads of Institutions Conducting Research with Public Health Service Grants

FROM : Surgeon General, Public Health Service

SUBJECT: Clinical research and investigation involving human beings

Expanding Public Health Service support of clinical research and investigation involving human beings emphasizes the need for more formal attention to the critical issues raised by such research.

In December 1965 the National Advisory Health Council, after study of these critical issues, made certain recommendations to me which I have now formulated as the following Public Health Service grant policy:

> No new, renewal, or continuation research or research training grant in support of clinical research and investigation involving human beings shall be awarded by the Public Health Service unless the grantee has indicated in the application the manner in which the grantee institution will provide prior review of the judgment of the principal investigator or program director by a committee of his institutional associates. This review should assure an independent determination: (1) of the rights and welfare of the individual or individuals involved, (2) of the appropriateness of the methods used to secure informed consent, and (3) of the risks and potential medical benefits of the investigation. A description of the committee of the associates who will provide the review shall be included in the application.

Effective immediately, this policy will be included in all future statements of Public Health Service research and research training grant policy. The wisdom and sound professional judgment of you and your staff will determine what constitutes the rights and welfare of human subjects in research, what constitutes informed consent, and what constitutes the risks and potential medical benefits of a particular investigation.

I wish to define more explicitly, however, what is meant by a committee of his institutional associates to assure an independent determination because the policy requires that the application include a description of the associates who will provide the review. The committee would need to be made up of staff of, or consultants to, your institution who are at the same time acquainted with the investigator under review, free to assess his judgment without placing in jeopardy their own goals, and sufficiently mature and competent to make the necessary assessment. It is important that some of the members be drawn from different disciplines or interests that do not overlap those of the investigator under review.

The policy does not ask for the names of the members of the committee. It does ask for a description of its composition; e.g., the number of members and the professional or public interests they reflect.

I have directed all my staff who administer the initial review of applications for grants for clinical research and investigation involving human beings -- regardless of whether these applications are for new, supplemental, renewal, or continuation support -- to ascertain that each application includes the information required by this policy and to obtain this information, whenever necessary, in a document signed by both the principal investigator or program director and the official for the institution.

I know that you are as deeply concerned with this issue as are any of us in the Public Health Service. I urgently request that you give my staff your cooperation in making this policy an effective instrument for the good of the public and science.

William H. Stewart

William H. Stewart, M.D.

U. S. Public Health Service
Division of Research Grants
Bethesda, Maryland 20014

PPO # 129
POLICY
February 8, 1966

SUBJECT : Clinical Investigations Using Human Subjects

APPLICABILITY : All PHS Research and Research Training Grants in Support of Such Clinical Investigations (including General Research Support Grants)

EFFECTIVE DATE: Immediately

BACKGROUND:

The National Advisory Health Council on December 3, 1965, recommended to the Surgeon General as follows:

> Be it resolved that the National Advisory Health Council believes that Public Health Service support of clinical research and investigation involving human beings should be provided only if the judgment of the investigator is subject to prior review by his institutional associates to assure an independent determination of the protection of the rights and welfare of the individual or individuals involved, of the appropriateness of the methods used to secure informed consent, and of the risks and potential medical benefits of the investigation.

The Surgeon General accepted the recommendation of the Council and instructed the Grants Policy Officer to develop implementing procedures for research and research training grants.

STATEMENT OF POLICY:

No new, renewal, or continuation research or research training grant in support of clinical research and investigation involving human beings shall be awarded by the Public Health Service unless the grantee has indicated in the application the manner in which the grantee institution will provide prior review of the judgment of the principal investigator or program director by a committee of his institutional associates. This review should assure an independent determination: (1) of the rights and welfare of the individual or individuals involved, (2) of the appropriateness of the methods used to secure informed consent, and (3) of the risks and potential medical benefits of the investigation. A description of the committee of associates who will provide the review shall be included in the application.

PROCEDURE:

The above policy becomes effective immediately and will be incorporated in all PHS research and research training grant regulations and research and research training policy statements as soon as possible. In the meantime, the attached memorandum from the Surgeon General explains the policy to grantee institutions.

The PHS staff who administer the initial review of applications for clinical research and investigation involving human beings (including the administrative review for continuation applications) shall ascertain that each application includes the information required by this policy and shall obtain this information, if necessary, in a document signed by both the principal investigator or program director and the official authorized to sign for the institution.

Attachment

ORIGINATING OFFICE: The Surgeon General, Public Health Service

APPROVED BY: Grants Policy Officer, OSG

Ernest M. Allen

Date: 2/8/66

Index: Clinical Investigations
Human Subjects: Clinical Investigations

APG.

MSCI 1860.2

May 12, 1966
effective date

MANNED SPACECRAFT CENTER

MANAGEMENT INSTRUCTION

ESTABLISHMENT OF MSC RADIOLOGICAL CONTROL MANUAL AND RADIOLOGICAL CONTROL COMMITTEE

1. PURPOSE

This Instruction establishes the MSC Radiological Control Manual (MSCM 1860) as the official medium for publication of procedures for control of atomic energy uses to satisfy U.S. Atomic Energy Commission (AEC) licensing regulations and MSC requirements, establishes a Radiological Control Committee, and prescribes responsibilities for exercising radiological control and establishing radiation protection regulations.

2. APPLICABILITY

The MSC radiological control policies and procedures apply to all MSC elements, all MSC contractor activities in facilities under MSC administrative control, and all MSC contractor development of hardware for use in spacecraft or in MSC facilities. Radiation protection regulations apply to any use of ionizing radiation in MSC facilities, and to uses at any location which are authorized by AEC licenses issued to MSC.

3. POLICY

It is the policy of MSC to exercise centralized control over the use of ionizing radiation sources and the approval of use programs to insure that exposure to radiation hazards and interface problems are properly controlled. Persons involved in the use of ionizing radiation are responsible for insuring compliance with AEC licensing constraints and radiation protection requirements.. All proposed uses of ionizing radiation, all procurement actions for sources of such radiation, and all facility and equipment design criteria for use of such radiation shall receive the signature approval of the chairman of the MSC Radiological Control Committee prior to issuance. Atomic energy applications which are licensed by the AEC and used on spacecraft in NASA manned space flight programs controlled by MSC shall be flown under the authorization of AEC licenses issued to MSC. Centralized control shall be exercised by the MSC Radiological Control Committee.

4. RADIOLOGICAL CONTROL COMMITTEE

a. The MSC Radiological Control Committee is established to:

(1) Coordinate and control uses of ionizing radiation.

(2) Review and approve all MSC radiological control policies and procedures.

(3) Develop and coordinate material to be incorporated in the MSC Radiological Control Manual.

(4) Serve as the Isotope Committee as defined by 10 CFR 30 (Title 10, Code of Federal Regulations, Part 30).

b. The Radiological Control Committee membership shall be designated by the Director and shall consist of the following:

Chairman:	Radiological Control Officer.
Executive Secretary:	A member of the Engineering and Development Directorate staff nominated by the Assistant Director for Engineering and Development.
Members:	Representative nominated by the Chief, Flight Safety Office.
	A minimum of three engineering or scientific representatives nominated by the Assistant Director for Engineering and Development.
	Representative nominated by the John F. Kennedy Space Center to serve as liaison and to be active on committee actions involving use of radioactive material at that Center under the authorization of AEC licenses issued to MSC.
Invited Observers:	Such representatives from Program Offices, White Sands Test Facility, other MSC organizations, or contractors, as may be requested and designated by the organization interested in a specific proposal before the Committee, or as requested by the Committee chairman.

c. Meetings will be held at the call of the Committee chairman.

5. MEDICAL USE SUBCOMMITTEE

a. The Medical Use Subcommittee of the Radiological Control Committee is established to:

(1) Review, from the standpoint of radiological health and safety, and initially approve or disapprove requests for use of radioactive material on humans or animals.

(2) Serve as the Medical Isotope Committee prescribed in Title 10, Code of Federal Regulations, Part 30, "to evaluate all proposals for research, diagnosis and therapeutic use of radioisotopes" in MSC programs.

(3) Coordinate and control any use of isotopes for medical purposes at MSC under a private practice or other organization license.

(4) Determine the adequacy of the training and experience of persons for human or animal use of a radioactive material for a specific purpose. Formulate and review training programs to qualify individual physicians assigned to MSC for categories of radioisotope uses.

b. The Medical Use Subcommittee membership shall be designated by the Chief of Center Medical Programs and consist of the following:

Chairman:	A physician from the medical staff of MSC.
Members:	A minimum of two other physicians, of whom one shall be expert in internal medicine, pathology, or hematology and another shall be expert in therapeutic radiology.
	A person experienced in assay of radioisotopes and protection against ionizing radiation.

6. TECHNICAL REVIEW SUBCOMMITTEE

a. The Technical Review Subcommittee of the Radiological Control Committee is established to:

(1) Review each proposed nonmedical use of radioactive material and radiation-producing devices to determine whether the proposed use and work is a part of the requesting organization's approved program, and whether the proposal is in accord with license provisions.

(2) Review proposed operational procedures to insure they are technically sound and that adequate radiological safety precautions have been specified.

(3) Provide recommendations and technical comments to the Radiological Control Committee on proposed uses; adequacy of facility and radiation area designs for intended use, qualification of personnel, and such other technical matters as may be referred to it by the Radiological Control Committee.

b. The Technical Review Subcommittee membership shall consist of the following:

Chairman:	Executive Secretary of the Radiological Control Committee.
Members:	One representative of Health Physics Section appointed by the Radiological Control Officer.
	One representative, a Radiological Control Coordinator, appointed by the Manager, Apollo Spacecraft Program Office.
	One representative, a Radiological Control Coordinator, appointed by the Manager, Gemini Program Office.
U.S. Gov't	One representative of each division of the Engineering and Development Directorate directly involved in Subcommittee actions, appointed by the division chief.
	One representative of the Engineering Division, appointed by the division chief.

7. CHAIRMAN, RADIOLOGICAL CONTROL COMMITTEE

The designation of the Radiological Control Officer as chairman establishes a staff position to implement the actions of the Committee and insure complete staff coordination. The chairman also serves as the Radiological Safety Officer, prescribed and defined in 10 CFR 30. This arrangement provides a central point for achieving accord between mission and radiation protection objectives. The chairman is responsible for:

a. Exercising general coordination and surveillance over the radiological control and radiation protection aspects of MSC operations.

b. Issuing material approved by the Radiological Control Committee for inclusion in the MSC Radiological Control Manual.

c. Issuing approval of radiation use requests in accordance with MSC Radiological Control Manual procedures.

8. EXECUTIVE SECRETARY, RADIOLOGICAL CONTROL COMMITTEE

The Executive Secretary is responsible for:

a. Reviewing radiation use requests to insure that they are properly planned and coordinated, supported by adequate technical data, and prepared in accordance with approved programs and functional assignments.

b. Preparing reports of Committee proceedings and maintaining official Committee records.

9. MANUAL CONTENT

The MSC Radiological Control Manual will establish detailed policies, procedures, standards, and guides to be followed in insuring proper radiological health and safety controls, compliance with AEC regulations, and the capability of MSC to secure and retain those types of AEC licenses which provide the necessary flexibility for operational requirements. The manual will cover the following subjects:

a. Special requirements and procedures for the acquisition, accountability, and control of radioactive material and radiation devices.

b. Functions and procedures of the Radiological Control Committee and subcommittees.

c. Radiological safety procedures and radiation monitoring.

d. Procedures for securing approval of work involving use of ionizing radiation, including use requests and special work permits.

10. ORGANIZATIONAL RESPONSIBILITIES

a. The Chief, Center Medical Office, is responsible for medical approval of proposals for developmental, experimental, evaluation or test uses of radiography and fluoroscopy on humans.

b. The Chief of Center Medical Programs is responsible for medical approval of proposed human and animal use of radioisotopes.

c. The Assistant Director for Engineering and Development is responsible for the performance of special engineering and physical tests and evaluations which may be required by the Radiological Control Committee to meet AEC requirements.

d. The Procurement and Contracts Division is responsible for insuring that proposed procurements involving sources of ionizing radiation have received Radiological Control Committee approval.

e. The Engineering Division is responsible for insuring that plans for construction or modification of facilities and equipment that involve storage or use of sources of ionizing radiation have received Radiological Control Committee approval.

f. The Radiological Control Officer is responsible for:

(1) Acting as the MSC liaison representative with the AEC, other NASA centers, and MSC contractors on matters of policy, approaches, and actions related to licensing and other regulatory functions applicable to the use of ionizing radiation.

(2) Developing and technically directing Health Physics services and special radiation effects analyses.

g. MSC elements are responsible for complying with mandatory provisions of the MSC Radiological Control Manual and following the guidelines contained therein.

II. RESCISSIONS

MSC Circular 41, Reference 2-4-8, dated May 31, 1963.

Robert R. Gilruth
Director

DISTRIBUTION:

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HHSC 90-7914

DEPARTMENT OF
HEALTH, EDUCATION, AND WELFARE
Public Health Service
Bureau of Medical Services
Silver Spring, Maryland 20910

June 23, 1966

Bureau of Medical Services Circular No. 38

CLINICAL INVESTIGATIONS USING HUMAN BEINGS AS SUBJECTS

1. PURPOSE. This circular specifies policy concerning clinical research and investigation involving human beings conducted in Bureau medical care facilities. It further establishes procedural requirements to assure that PHS research on human beings is ethically and morally exemplary.

2. BACKGROUND. The National Advisory Health Council on December 3, 1965, recommended to the Surgeon General as follows:

> "Be it resolved that the National Advisory Health Council believes that Public Health Service support of clinical research and investigation involving human beings should be provided only if the judgment of the investigator is subject to prior review by his institutional associates to assure an independent determination of the protection of the rights and welfare of the individual or individuals involved, of the appropriateness of the methods used to secure informed consent, and of the risks and potential medical benefits of the investigation."

3. POLICY. The Surgeon General accepted the recommendation of the Council and adapted it in the following PHS policy statement:

> "No clinical research and investigation involving human beings shall be conducted by Public Health Service personnel or by PHS contractors without (1) prior review of the judgment of the principal investigator or program director by a committee of his associates not directly involved in the research and (2) prior written approval by the Bureau Chief or by the Institute Director if the Bureau Chief formally delegates the responsibility to him. This review should assure an independent consideration: (1) of the rights and welfare of the individual or individuals involved, (2) of the appropriateness of the methods used to secure informed consent, and (3) of the risks and potential medical benefits of the investigation. Each study protocol along with the names and recommendations of the review committee and the written

approval of the Bureau Chief (or his official delegate) will be placed on file in the office of the Division responsible for the study before the study is initiated."

4. PROCEDURE. Effective immediately:

a. This policy shall be included in all future statements of Bureau research policy. It shall be included in all applications to NIH for research grants, and in all protocols, covering research projects involving human beings.

b. Field and headquarters research committees shall take cognizance of the following criteria in their review of research study proposals which will involve human beings:

(1) The investigation must have an anticipated value or benefit to mankind that outweighs the risks involved to the human participants. In no event shall the investigation knowingly or deliberately involve undue physical or mental discomfort or the likelihood of death or of permanent injury or incapacity.

(2) Each human subject shall have a completely free choice to participate or not participate in any investigation and a free choice to terminate his participation at any time during the investigation.

(3) No human being should be accepted for any investigation unless:

(a) He has first been informed of the kind or nature of, and the reasons for, the treatment or procedures to which he will be subjected and of the known and possible hazards, disadvantages and discomforts involved both during and following his participation; and

(b) His consent to participate is reduced to writing and is in such form as will indicate on its face that he has been fully informed of, and voluntarily accepts, the risks involved.

(4) If the human subject is a patient who has been admitted for treatment by the Service, he shall not be permitted to participate in an investigation unless either:

(a) The investigational procedure has no relation to the illness for which he is under treatment and his participation will have no adverse effect on the course of his illness or its treatment either by interfering with, postponing, or any other way affecting, his progress and the standard or customary course of treatment;or

(b) The investigative procedure is intended and designed to improve the condition for which he is being treated and he is fully informed of his right either to reject or refuse the treatment or procedure under investigation and to receive the standard or customary treatment, or to elect in writing to accept the treatment under investigation.

(5) No subject may participate in an investigative procedure unless:

(a) He is mentally competent and has sufficient mental and communicative capacity to understand his choice to participate; and

(b) He is 21 years of age or more, except that if the individual be less than 21, he may participate in a procedure intended and designed to protect or improve his personal health or otherwise for his personal benefit or advantage if the informed written consent of his parents or legal guardian be obtained as well as the written consent of the subject himself if he be mature enough to appreciate the nature of the procedure and the risks involved.

(6) Both appropriate staff and equipment resources must be available at the place the investigation is to be conducted to give all possible aid and treatment in the event the human subject suffers an accident or an adverse reaction while participating in, or as a consequence of, the investigation.

(7) The investigation must be conducted only by investigators qualified by scientific and medical training and experience to conduct the type of study involved and having the competence required to protect the well-being and safety of the subject; they and their subordinates assisting in the investigation must also be knowledgeable of the possible reactions and how to cope with them.

(8) Immediate reports of any untoward events harmful to participants and arising in the course of the investigation shall be made by the investigator to the review committee for the project involved such committee shall retain responsibility to terminate any investigation if the risks developing appear to outweigh potential benefits or where, for any reason, further conduct of the investigation is not considered justified.

5. DELEGATION. The authority to approve research projects involving human beings to be conducted in Bureau facilities is hereby delegated to the appropriate Division and Program Chiefs and their Deputies. Research

study protocol files are to be maintained in the Division and Program headquarters.

6. EFFECTIVE DATE. The provisions of this Circular are effective immediately.

Carruth J. Wagner, M.D.
Assistant Surgeon General
Chief, Bureau of Medical Services

Sir + L.T. Thacker

C
O
P
Y

October 11, 1966

James L. Goddard, M.D.
Commissioner of Food and Drugs
Department of Health, Education, and Welfare
Washington, D.C. 20204

Dear Commissioner Goddard:

Since my letter to you of September 1 and your reply of September 19, representatives of our member firms have given extended consideration to the August 30 Federal Register (31 FR 11415) order entitled "Consent for Use of Investigational New Drugs on Humans; Statement of Policy."

The comments in this letter and the enclosed memorandum, setting forth the reasons for our legal opinion that many provisions of the order exceed the authority vested in the Food and Drug Administration by the portion of Section 05(i) dealing with patient consent, reflect the position of the Pharmaceutical Manufacturers Association with regard to the order.

The August 30 statement, in our opinion and in the opinion of many physicians and scientists, imposes conditions upon the investigator with which he is physicially unable to comply; it requires a subject or patient to make medical decisions which he lacks the capacity to make; it produces an unwarranted interference with the doctor-patient relationship; it prevents the conducting of meaningful double-blind studies; it will increase the number of medically unfounded professional liability suits; it makes it more difficult to obtain U.S. and foreign clinical investigators; it will lengthen the time required to get new life-saving drugs to the public; it will increase the cost of new products; and because of its ambiguity and inconsistent use of terms, many questions are raised as to its meaning and purpose.

Informed consent, as defined in para. (h) of the Order, requires imparting to the person involved "a fair explanation of all material information concerning the administration of the investigational drug, or his possible use as a control." The investigator must inform the person (among other things) of "the nature, duration and purpose" of the drug, "the method and means of administration", "all inconveniences and hazards reasonably to be expected, including the fact, where applicable, that the person may be used as a control, the existence of alternate forms of therapy, if any, and the effects upon his health or person that may possibly come from the administration of the investigational drug." (Emphasis added)

It is impossible, we submit, to meaningfully convey to a layman all the information required by this definition. It is often unknown by the investigator how long the medication will be administered. To convert all the scientific data in the clinical brochure into lay terms and inform each person is a monumental task even assuming a layman could comprehend it. Multiply this by the alternate forms of therapy and the impossibility of compliance becomes clear.

The investigator under the statement is charged with the responsibility of deciding whether the patient or subject is actually informed and has made a wise medical choice. We do not comprehend how an investigator will be capable of imparting the results of his own years of education and training (and experience with "alternate" drugs) so completely that each and every patient, no matter how untrained, will be in a position to capably refute or confirm the physician's medical judgment.

The definition of informed consent in the statement of policy is apparently an attempted codification of the mass of civil case law governing such consent as it applies to the administration of established drugs. Entirely apart from the failure of the order (indeed, the impossibility of it) to reflect the status of the law in that area, the requirements of what constitutes informed consent with regard to old well-known drugs cannot be applied to the administration of investigational new drugs. In the latter category, much of the information required to be imparted by the statement is unknown. This is especially so with regard to drugs involved in phase one and two studies.

In addition to the mass of information that must be imparted under the Order to a patient before obtaining his consent, the practical elimination of the discretion provided by the 1962 Amendments and which civil law has long granted the physician to decide when, in his patient's best interest, consent should or should not be obtained, is an unwarranted invasion into the physician-patient relationship which will work to the detriment of the individual patient.

The Order requires clinical investigators in clinical studies to obtain consent from every subject to whom an investigational new drug is "administered primarily for the accumulation of scientific knowledge, for such purposes as studying drug behavior, body processes, or the course of a disease." In addition, consent must be obtained in all but "exceptional cases" from patients "under treatment" with investigational drugs. Under treatment is restricted to situations where administration of the drug "constitutes responsible medical judgment taking into account the availability of other remedies or drugs and the individual circumstances pertaining to the person to whom the investigational drug is to be administered." A patient is defined as one "under treatment." The definition of "under treatment" at the very least, places all subjects in phase one and phase two studies in the role of those to whom the drug is "administered primarily for the accumulation of scientific knowledge", and from whom as noted consent must be obtained in <u>every</u> case. It may even have been intended by the restrictive definition to prohibit

treatment of a patient (as opposed to a subject) in phase 3 studies.

The exceptional cases justifying a physician not obtaining consent from a patient under treatment (which exceptional cases are to be strictly applied), are cases where it is "not feasible" to obtain consent or where obtaining consent would be "contrary to the best interest of such human beings." "Not feasible" is limited to cases where the investigator is not capable of obtaining consent because of his inability to communicate with the patient or his representative. The term "not feasible" (which in Webster's Seventh New Collegiate Dictionary, G&C Merriam Co., Springfield, Mass., 1965, at page 432 is listed along with impracticable as a meaning for infeasible) thus is equated in the statement of policy with impossibility. It should also be noted that it is the patient who is not capable of giving consent rather than the investigator being incapable of obtaining it.

"Contrary to the best interests of such human beings" is restricted to situations where "the communication of information to obtain consent would seriously affect the patient's disease status" (emphasis added). Thus, a physician is required to obtain consent where the disease status would not be affected though the patient's mental state could be seriously impaired.

To enable a patient to receive the best treatment individually suited to his needs, a physician must be allowed discretion in deciding what information, if any, should be imparted. There are many factors that enter the decision. Among the circumstances to be considered are: the type of disease or diseases the patient is suffering, his mental, physical, and emotional state as well as his age and intelligence, and the nature of the drugs involved.

The effect of implementation of the policy statement on meaningful double-blind studies will certainly be adverse. The requirement that the patient be advised that he might be given a control or a placebo will have an undeterminable effect on his reactions. Placebo reactors play a large part in the evaluation of double-blind testing. One of the major reasons for such studies is to reduce the number of placebo reactors. Many persons will refuse to participate in a study if made aware of the possibility that they will receive a placebo when other known therapeutic remedies are available.

The impossibility of compliance with the order described above will necessarily result in an increase in medically unfounded medical professional liability suits. The view has been expressed that physicians, in order to protect themselves, from both FDA action and malpractice suits will have to prepare lengthy self-serving memoranda to protect themselves in situations where they determine that consent should not be obtained. More than one attorney has stated that the only advice he can give investigators in the light of the policy statement, is to discontinue new drug clinical trials. We have been informed that some clinics have already decided to cease conducting clinical trials.

In the last few years, many Canadian investigators have refused to sign the U.S. clinical investigation forms because of the administrative burdens involved. The problem can be expected to become acute in Canada and in other countries as a result of the subject statement. Increased difficulty can also be anticipated in obtaining capable U.S. clinicians in the face of the manifold problems in attempting to comply with the order. Consequently, more dealys in obtaining new drug application approvals and additional costs would seem to be an inevitable result if the new statement of policy remains in effect.

There have been many questions brought to our attention concerning the meaning of the order. Examples are: Why is the consent of a patient under treatment required to be in writing when the consent of one administered the drug primarily for the accumulation of scientific knowledge need only be oral? Is it sufficient that the written consent be only an acknowledgement that a fair explanation of all material information had been made or must it include a recital of such information? Why is the consent of a patient under treatment required to be in writing when the consent of his representative need only be oral? Why must the investigator himself necessarily be the person to render a fair explanation of all material information? What effect do the provisions in the policy statement have on studies in progress on August 30? What effect do the provisions of the policy statement have on studies in foreign countries? To what degree is the sponsor legally responsible if an investigator submits a complete form FD 1572 or 3 and then does not obtain informed consent? Is it FDA's intention to change (either by regulation or by other means) forms FD 1572 or 3 to incorporate the new statement? Will FDA inspectors inspect consent forms? Under the regulation, how will an investigator be able to treat a terminal cancer patient with an investigational new drug without informing such patient of his condition? Is it the intention of FDA that double-blind studies are no longer required or desired?

We realize, and are in full accord with the position, that the health of patients is the first consideration of a physician. We are, in addition, in agreement with the congressional mandate that consent be gained from both patients and subject except where not feasible, or in the judgment of the investigators not in the best interests of such person. The August 30 statement of policy, however, serves only to confuse the patient, the investigator, and the sponsor.

The Declaration of Helsinki, prepared by the World Medical Association, has been gaining increasing acceptance throughout the world, including endorsement by many of our leading medical and research societies. Its provisions and similar safeguards, as well as other possible alternatives, should be carefully considered before unrealistic guidelines are imposed by the Food and Drug Administration.

It is respectfully requested that enforcement of the statement of policy be held in abeyance pending consultation with those most directly involved. Repre-

sentatives of medical associations and societies and of the Pharmaceutical Manufacturers Association and its member firms stand ready to assist in any way in the formulation of revised guidelines which will still assure the well being of persons and subjects used in pharmacologic and clinical trials.

Sincerely,

/s/ C. Joseph Stetler

Enclosure

MEMORANDUM

Regarding Statement Appearing in August 30, 1966 Federal Register Concerning Clinical Investigation of Drugs

Section 505(i) of the Federal Food, Drug and Cosmetic Act provides, in part:

> ". . . Such regulations shall provide. . . . the manufacturer requiring that experts using such drugs for investigational purposes certify . . . that they will inform any human beings to whom such drugs, or any controls used in connection therewith, are being administered, or their representatives, that such drugs are being used for investigational purposes, and will obtain the consent of such human beings or their representatives, except where they deem it not feasible, or in their professional judgment, contrary to the best interests of such human beings."

The function of the "August 30 statement of policy" is apparently to set forth the Food and Drug Administration's interpretation of the requirements embraced in the above quoted statutory language. See subsection (a) and (b) of the Statement of Policy. Without considering the necessity or propriety of giving interested persons an opportunity to comment on such a statement, it is basic law that such regulations are only valid in so far as they are a reasonable interpretation of the statutory language. They may not increase the scope of the statute.

The quoted statutory provision imposes a duty upon a manufacturer of an investigational new drug to require investigators to inform human beings that the drugs or controls administered "are being used for investigational purposes and . . . obtain (the) consent" except where they deem it not feasible or in their professional judgment contrary to best interests of such human beings. The consent referred to is that the patient or subject will permit administration of the drug though he knows it is an investigational new drug. Nothing is said in the statute about conveying all the information that civil and (or) state law may require prior to the administration of established drugs. The reason is obvious. Such comprehensive data is usually not known concerning investigational drugs. This is why they are under investigation. The statements by members of Congress on the floor, describing the consent provisions, in no way indicate that the "informed consent" concept set forth in the regulation was intended by the amendment. Representative Chet Holifield of California, in discussing the so-called Friedel Amendment to H.R. 11581, 87th Congress, (containing the same language as quoted above) stated on the floor of the House of Representatives on September 27, 1962:

> "If a doctor is going to do any experimenting on me, I would like to know that it was an experiment. I might agree and probably would if my doctor said 'Now, we do not know what the result of this will be, but we think it will be very good, we are hopeful.' " (Congressional Record, 87th Congress,

Second Session, Page 19889)

During the same interchange, Representative Paul Rogers of Florida stated, "I think at the present time ethics require a doctor to notify a patient before he uses an experimental drug. However, there are cases that have been pointed out where there may be a situation where consent cannot be obtained . . . ." (Congressional Record, supra, p. 19889)

The statute provides that it is not necessary to obtain consent if the investigator (rather than the Food and Drug Administration) using his professional judgment decides that it is not feasible or not in the best interests of the patient or subject. As stated by the late Senator Estes Kefauver of Tennessee in response to a request for clarification of this provision:

> "On the Senate floor an amendment was offered and accepted to the effect that in giving experimental drugs, physicians shall consider the best interests of their patients. In the House of Representatives, the Friedel Amendment, which was along the same line but somewhat tighter, was adopted. In conference, an amendment in line with these two amendments -- suggested by the Senator from Nebraska -- was submitted. I proposed some rearrangement of the language, but there was no change in the meaning. The resultant language requires the patient's consent, except in instances -- as the Senator from New York has said -- in which it is deemed not feasible as in the doctors best judgment is contrary to the best interests of such human beings. The decision must be according to the best judgment of the doctors involved. There will be no interference with the doctor-patient relationship. But the responsibility for not obtaining the patient's consent will clearly rest with the physicians. (Congressional Record, supra, p. 22042.)

Several statements made by other Senators and Congressmen to the same effect also appear in the Congressional Record, supra, pp. 16337, 16341, 16343 and 19889. There is absolutely no basis either in the statute or in its legislative history for the Food and Drug Administration to dictate the circumstances under which an investigator need or need not obtain consent. Indeed, amendment 8-22-62.A to S. 1552, 87th Congress, 2nd Session, proposed by Senator Jacob Javits of New York on August 23, 1966, would have authorized the Secretary of Health, Education, and Welfare to promulgate the exceptions to the obtaining of consent rules. This approach, however, was dropped in favor of the present provision. It is worthy of note that several Congressmen and Senators specifically mentioned that an investigator should be allowed to exercise discretion regarding patients with serious disease, who do not know about them and patients who might suffer adverse mental or emotional reactions. (Congressional Record, supra, pp. 16335, 16336, 16337, 16339, 19889.) Recognition was given that informing persons in those circumstances might be contrary to their best interests. The August 30 Policy Statement on the other hand restricts such discretion to cases where "the communication of information to obtain consent would seriously affect the patient's disease status."

The legislative history is barren of any Congressional intent to limit the application of the phrase "not feasible" (which is equated by Webster's Seventh New Collegiate Dictionary, G. C. Merrian Co., 1965, with impractible at page 432) so that it means "impossible", as is done in the Statement.

There is nothing in the statute or the legislative history which distinguishes between subjects and patients nor is there any indication that the consent involved need be obtained in writing.

It is probable that the Policy Statement represents an attempt by the Food and Drug Administration to "codify" the malpractice and state laws regarding informed patient consent. No such responsibility has been placed upon the Agency by the Congress. It is beyond the realm of reason to propose that the authority to interpret the meaning of a federal statute includes the authority to codify the vast and conflicting body of law created by federal and state courts decisions.

It has long been recognized by the Food and Drug Administration that the provisions in Section 503(b) of the Federal Food, Drug and Cosmetic Act, restricting the prescribing of certain classes of drugs to "practitioners licensed by law", mean that such drugs may be prescribed only by practitioners in each state who are such in accordance with the law of that state. It has been admitted that FDA has no authority to regulate who may practice medicine. The same rule applies to patient consent. Administrative fiat cannot be employed to dictate the physician-patient relationship or other principles of the practice of medicine.

Although affected persons are entitled by law to ignore an interpretive regulation which is not a valid construction of the statute and will be protected by proving that fact in any court action instituted by the agency; such protection is meaningless in the instant case.

Sections 130.3(a)(12) and (13) of the new drug regulations require that the sponsor obtain from each investigator signed statements including a certification by each investigator that [1] "will inform any patients or any persons used as controls, or their representatives, that drugs are being used for investigational purposes, and will obtain the consent of the subjects, or their representatives, except where this is not feasible or, in the investigator's professional judgment, is contrary to the best interests of the subjects."

Presumably, the policy statement "interpretations" now "apply" to those sections. The sponsor must include in his "notice of claimed investigational exemption for a new drug" a statement that he has obtained such certification (Regulation 130.32)

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1) The quotation that follows is from form FD 1572 governing phase 1 and 2 investigations. It is interesting to note that the requirement for phase 3 (form FD 1(contains identical wording with one exception. The phase "inform any patients a persons used as controls" is replaced by "inform any subjects, including subject used as controls" even though there are no patients in phase 1 studies and a large number of patients in phase 3 trials.

There is no requirement that the sponsor forward copies of these statements to FDA or that the investigators retain copies. However, FDA Inspectors may inspect the sponsors' records (Regulation 130.3(a)(5) and 130.11) as well as the investigators' (130.3 (a) (12) and (13)). The Food and Drug Administration may "blacklist" an investigator who "repeatedly or deliberately fails (ed) to comply with the conditions of the exempting regulations" (130.(c)) and may revoke a sponsor's exemption for investigational use if "the clinical investigations are not being conducted in accordance with the plan submitted in the 'Notice of claimed investigational exemption for a new drug' " (Regulation 130.(d)(7)). This becomes especially important in view of the decision in Turkel v. Food and Drug Administration, 334 F2d 844 (C.A.6, 1964) that the revocation of an investigational new drug exemption is not reviewable in the United States Circuit Court of Appeals.

Thus, although the statement of policy does not have the force and effect of law from the point of view of legal theory, FDA presumably could take far reaching administrative action without affording interested parties their day in court.

Accordingly, the August 30 Policy Statement should be revoked.

American Medical Association
535 NORTH DEARBORN STREET • CHICAGO, ILLINOIS 60610
AREA CODE 312
527-1500

F. J. L. Blasingame, M.D.
Executive Vice President
Ernest B. Howard, M.D.
Assistant
Executive Vice President

September 28, 1966

James L. Goddard, M.D.
Commissioner of Food and Drugs
Food and Drug Administration
Washington, D.C.

Re: Consent for Use of Investigational New Drugs on Humans; Statement of Policy (21 CFR 130.37).

Dear Commissioner Goddard:

We have given careful consideration to the "new statement of policy" governing consent for use of investigational new drugs on humans which appeared in the August 30 issue of the Federal Register, and submit herewith our comments.

Section 505(i) of the Federal Food, Drug, and Cosmetic Act provides that regulations on the use of investigational new drugs shall impose the condition that investigators "obtain the consent of such human beings or their representatives, except where they deem it not feasible or, in their professional judgment, contrary to the best interest of such human beings." There is nothing in that Section which grants the Food and Drug Administration authority to impose its opinion of what constitutes consent upon the medical profession. The "consent" provision was enacted as a measure to assure that medical practitioners protect the human rights of individuals in the investigation of new drugs. These rights do not emanate from the Food, Drug, and Cosmetic Act -- to be defined, amplified, or interpreted by the Commissioner. They exist in the entire body of civil law.

It is impossible for the Commissioner to codify realistically, in the form of a policy statement, the legal requirements for valid consent under the myriad varying circumstances which

exist. There are thousands of pages of case law which perform that function. The court in each case does and must take into account the particular fact pattern involved. Also considered is the discretion that must be left with the individual practitioner if he is to be able to best serve his patient. The manner in which the proposed regulation has been drafted makes it appear that FDA, in one policy statement, is attempting a codification of that entire body of law. For example, the comprehensive criteria set forth as necessary for an "informed consent" are seemingly derived from recent court decisions. Yet, among other things, it would appear from the statement that a "representative" has unlimited legal authority to give valid consent to the administration of investigational drugs to a child or institutionalized incompetent person, etc., primarily for the accumulation of scientific knowledge.

From the standpoint of proof it may be better, if the need arises, for the physician to have the patient's consent in writing. However, the requirement that such consent shall be in writing exceeds existing legal requirements for a valid consent and constitutes an unwarranted interference with the practice of medicine. The use of investigational drugs does not always involve unusual hazards, and it should be left to the physician's discretion as to whether a written rather than an oral consent should be obtained.

In providing that the "patient's consent shall be obtained in writing by the investigator" is it intended that written consent shall be obtained only in the case of a patient but not a subject? Is it intended that written consent shall be obtained from a patient, but oral consent is sufficient when a representative acts on his behalf? Is it necessary that the patient's written consent be obtained only by the investigator, or can it be obtained by someone else? Does the "fair explanation of all material information" have to be stated in the written consent, or will a simple statement of consent to the administration of the investigational drug suffice?

James L. Goddard, M.D. September 28, 1966

In our opinion, the policy statement exceeds the authority delegated to the Commissioner, contains ambiguities which would result in confusion concerning the legal responsibilities of physicians in the investigational use of new drugs, and is an unwarranted interference with the practice of medicine. We urge, therefore, that it be withdrawn. In any event, we request that its effectiveness be stayed until representatives of the various interested organizations and the FDA have had a full opportunity to discuss the statement and explore alternatives.

Respectfully submitted,

F. J. L. Blasingame

F. J. L. Blasingame, M. D.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
5600 ROCKVILLE PIKE
BETHESDA, MD. 20014

December 12, 1966

TO : Heads of Institutions Receiving Public Health Service Grants

FROM : Surgeon General, Public Health Service

SUBJECT: Clarification of procedure on clinical research and investigation involving human subjects

The attached report of December 12, 1966, on the above subject, is to clarify issues raised by Public Health Service grantees and staff since the issuance by this office of PPO #129, Revised, dated July 1, 1966, subject: "Investigations Involving Human Subjects, Including Clinical Research: Requirements for Review to Insure the Rights and Welfare of Individuals."

This policy refers to all investigations that involve human subjects, including investigations in the behavioral and social sciences. It does not reflect a change in policy, but is a clarification only of the current policy for the use of grantees.

William H. Stewart

William H. Stewart, M.D.

Attachment

U. S. Public Health Service
Division of Research Grants
Bethesda, Maryland 20014

December 12, 1966

SUBJECT : Investigations Involving Human Subjects, Including Clinical Research: Requirements for Review to Insure the Rights and Welfare of Individuals: Clarification

APPLICABILITY: All PHS Grants and Awards

REFERENCE : PPO #129, Revised, July 1, 1966

This report is to clarify issues raised by PHS grantees and staff regarding the meaning of the requirements of PPO #129, Revised, July 1, 1966, subject: "Investigations Involving Human Subjects, Including Clinical Research: Requirements for Review to Insure the Rights and Welfare of Individuals."

This policy refers to all investigations that involve human subjects, including investigations in the behavioral and social sciences. The grantee institution is responsible for assuring that the investigations are in accord with the laws of the community in which the investigations are conducted and for giving due consideration to pertinent ethical issues. Appropriate groups of associates within the institution, and outside consultants if needed, are to be utilized to provide the necessary review. Institutions may designate separate groups in order to assure competence and independence of review for particular areas.

The principles of this policy apply most directly and comprehensively in those instances of social, behavioral, and medical science investigations where a procedure may induce in the subject an altered state or condition potentially harmful to his personal welfare. Surgical procedures, the administration of drugs, the requirement of strenuous physical exertion, and participation in psychologically or socially harmful activities are examples of experimental arrangements which require thorough scrutiny by institutional review groups. Such procedures require continuing overview and full documentation for the record.

Aside from the above types of procedures, there is a large range of social and behavioral research in which no personal risk to the subject is involved. In these circumstances, regardless of whether the investigation is classified as behavioral, social, medical, or other, the issues of concern are the fully voluntary nature of the participation of the subject, the maintenance of confidentiality of information obtained from the subject, and the protection of the subject from misuse of the findings. For example,

a major class of procedures in the social and behavioral sciences does no more than observe or elicit information about the subject's status, by means of administration of tests, inventories, questionnaires, or surveys of personality or background. In such instances, the ethical considerations of voluntary participation, confidentiality, and propriety in use of the findings are the most generally relevant ones. However, such procedures may in many instances not require the fully informed consent of the subject or even his knowledgeable participation. In such instances full and specific documentation is necessary for the record.

Many investigations in the social and behavioral sciences involve procedures designed to alter the status of the individual as, for example, studies of human learning, social perception, or group effectiveness. In such research the effects, if any, on the subject may be transitory or even more or less permanent, but they must be judged clearly not to be harmful or not to involve the risk of harm.

Whatever the nature of the investigation, the concern for the protection of the subject and for the assurance of voluntary participation becomes most critical when the subject is not of age or competence to make an adequate judgment in his own behalf.

These are only some examples of issues which may arise. The fundamental point is that every project must be considered on an individual basis to clarify which, if any, such issues are present and to insure that these are adequately resolved by the specific design of its procedures. For this reason, it is essential that the grantee institution be responsible for the clarification and resolution of all ethical and other pertinent issues. The appropriate mechanism for this purpose is the utilization of groups of associates, established at the institution to provide competent, independent review. Based on its knowledgeable scrutiny of the specifics of the investigation involved, such a review group can decide which issues are germane and ascertain the adequacy of provisions for protecting the rights and welfare of human subjects in research, the appropriateness of the methods used to secure informed consent, and the risks and potential benefits of the investigation.

ORIGINATING OFFICE: Office of the Director, Division of Research Grants

APPROVED BY: Grants Policy Officer, OSG

Ernest M. Allen

Date: 12/15/66

Index: Clinical Research
Human Subjects: Behavioral Investigations
Clinical Investigations
Medical Science Investigations
Social Science Investigations

DOE-1214.4-C Sample

OAK RIDGE ASSOCIATED UNIVERSITIES
Oak Ridge, Tennessee

C#6 132

Patient Admittance Agreement

The Oak Ridge Institute of Nuclear Studies (ORINS) Medical Research Hospital is operated by Oak Ridge Associated Universities (ORAU) for the U. S. Atomic Energy Commission (AEC) for the conduct of certain clinical research programs. These programs are mainly in areas allied to the application of radiation and radioisotopes to medicine and other health sciences.

I understand that I have been accepted as a patient for admission to the hospital, or as an outpatient, because my physical condition has been determined by the hospital staff to make me a suitable patient for a currently active clinical research project.

I further understand that while a patient at the research hospital examinations, treatments, and tests may be prescribed which are experimental in nature and I hereby consent to such examinations, treatments, or tests. Notwithstanding the above, I reserve the right to a full explanation of any such proposed examination, test, or treatment and the right to withdraw my consent. I further reserve the right to withdraw completely should I find that I am unable to continue.

I further understand that I can remain in the research hospital only so long as I am needed for research purposes, and that I must be discharged when my participation in a study is completed and when, in the opinion of the hospital staff, my medical condition permits. In such event, I understand that ORAU, its officers, employees, and agents, cannot assume responsibility for any continued medical care.

The above statements have been explained to me by the member of the Medical Division staff named below. I understand and accept the statements.

I have not been influenced in making this agreement by any representations or statements regarding improvement in my physical condition or the probable results of any treatments received, but instead expressly assume all risks incident to my hospitalization, care, and treatment.

Patient's signature	Medical Division staff member's signature
Parent or guardian's signature	Date

PATIENT ADMITTANCE AGREEMENT MED-13(2-67)

OAK RIDGE ASSOCIATED UNIVERSITIES
Oak Ridge, Tennessee

Consent to Experimental Treatment

I authorize the performance upon _____ (myself or name of patient)
of the following treatment: _____

_____

_____
(State nature or treatment)

The nature and purpose of the treatment, possible alternative methods of treatment, the risks involved, and the possibilities of complications have been explained to me. I understand that this treatment is not the usual treatment for my disorder and is therefore experimental and remains unproven by medical experience so that the consequences may be unpredictable.

DATE: 70 _____
(Patient or person authorized to consent for patient)

WITNESS: _____

_____

I have talked with _____ about
Name
the proposed course of treatment to be given _____
Name
including the following:* _____

_____

_____ 7[illegible]
Physician Date

*Physician should indicate experimental drugs, radioisotopes, radiation therapy, and/or possible placebo or sham therapy.

CONSENT TO EXPERIMENTAL TREATMENT MED-146(2-67)

OAK RIDGE ASSOCIATED UNIVERSITIES

Oak Ridge, Tennessee

Authorization for the Administration of Radioactive Substance

I hereby authorize the staff of the ORINS Medical Division to administer to _____ the following radioactive substance _____ _____
Nuclide Chemical

_____ _____
Dose Route of administration

The purpose of this procedure has been explained to me as being:

_____

_____

_____

Its relevance to my condition, the risks and any possible alternatives have been explained to me.

_____
Name of patient

_____ 67
Date

AUTHORIZATION FOR THE ADMINISTRATION OF RADIOACTIVE SUBSTANCE MED-148(2-67)

[illegible] interests in the unofficial status. [illegible] are reminded of the requirement [illegible] article 1252.4 of NAVMATINST to submit one copy of each published article to NAVMAT.

20-7. Navy Laboratory Funds (Independent Research)

(1) *Objectives.*—The principal objectives of the Navy Laboratory Funds Program are to enhance the competence of a laboratory; permit it to grow in scientific stature; improve its ability to attract competent investigators; initiate challenging work and ultimately improve its capability to make new ideas and fresh approaches pay off in terms of its directed programs.

(2) *Funds.*—Subject to the current availability of funds, BUMED will provide major research and development command activities with Navy Laboratory Funds to conduct independent research. The Funds will be furnished to provide flexibility for the investigation of new ideas generated during the year for which there is no provision for funding in the formal program. The Navy Laboratory Funds will be in addition to those provided for approved or assigned work units, and since they are primarily to augment and exploit technical competence, they shall not be used to make up deficits in directed parts of the program, nor normally to sponsor contract research.

(3) *Controls.*—Prior BUMED approval is not required for studies undertaken with these funds. The commanding officer of the laboratory will direct the use of these funds and may set up a board of senior investigators to assist him in the selection of studies to be conducted. These studies should normally have a 2-year limitation, to be extended only with specific BUMED approval. Projects showing promise shall be incorporated into the regular research or development program at any time by submitting them as a proposal in accordance with article 20-6(4).

(4) *Report.*—Activities provided Navy Laboratory Funds shall submit a letter report, Report of Independent Research Funds (Report Symbol MED 3920-1), to reach BUMED (Code 71) no later than 15 July each year. The reporting period shall be the fiscal year in which funds are received. The content of the report shall include the identification of studies undertaken, progress or results, and obligations and expenditures against the studies.

20-8. Use of Volunteers in Medical or Other Hazardous Experiments

(1) *Approval.*—Experimental studies of a medical nature or experiments which pose any unusual hazard to the subjects are forbidden except when the study or experiment, and the use of volunteer human subjects, has been approved by the Secretary of the Navy. Such studies or experiments shall be approved via their chain of command. In each case the experimental design and medical support shall be reviewed by the Chief, BUMED, to determine the adequacy of the safety factor.

(2) *Volunteer Policy.*—Participation shall be on a volunteer basis only. Volunteers, after full information, shall consent in writing but shall not be required to execute a release from future liability for negligence attributable to the Navy.

(3) *Administrative Procedures.*—Requests for the use of volunteers as subjects for medical or other potentially hazardous experiments shall be submitted in accordance with SECNAV Instructions and such implementing Instructions as may be promulgated by lesser authority.

(4) *Record.*—For each instance a statement shall be entered in the individual's medical record indicating the work-unit number and title, and a notation of the physical and/or psychological effect, or lack of same, resulting from the investigation.

20-9. Experimental Animals

(1) Department of Defense Instruction 3216.1 of 19 April 1966 established the policy governing the use and care of experimental animals involved in the research, development, test, and evaluation programs of DOD Components, and also certain public information aspects pertaining thereto. Pertinent portions are quoted below for compliance:

III. *POLICY.* The Department of Defense is one of the Federal agencies which, along with the scientific community and a majority of the United States public, supports the use of experimental animals in research in contributing toward the achievement of national defense objectives and to the public welfare. It is anticipated that investigations with experimental animals in support of national defense requirements will increase because of the widening scope of military operations. Despite general acceptance, the use of animals in research has proved to be a sensitive subject among various groups in the United States and foreign countries. For this reason the following policy is enunciated:

A. On the Care of Experimental Animals

1. All aspects of investigative programs involving the use of laboratory animals sponsored by DoD Components will be conducted according to the principles enunciated in the "Guide for Laboratory Animal Facilities and Care," (ref. (c)). This guide represents the views of the American professional groups in the life sciences.

2. Laboratory staffs and facilities shall in all cases be sufficient to meet the high standards desired, including the provision of all necessary support services such as veterinary care and trained service personnel, and

20-6 Use of Volunteers in Medical or Other Hazardous Experiments

(1) Approval. — Experimental studies of a medical nature or experiments which pose any unusual hazard to the subjects are forbidden except when the study or experiment, and the use of volunteer human subjects, has been approved by the Secretary of the Navy. Such studies or experiments shall be approved via their chain of command. In each case the experimental design and medical support shall be reviewed by the Chief, BUMED, to determine the adequacy of the safety factor.

(2) Volunteer Policy — Participation shall be on a volunteer basis only. Volunteers, after full information, shall consent in writing but shall not be required to execute a release from future liability for negligence attributable to the Navy.

(3) Administrative Procedures. — Requests for the use of volunteers as subjects for medical or other potentially hazardous experiments shall be submitted in accordance with SECNAV Instructions and such implementing Instructions as may be promulgated by lesser authority.

(4) Record. — For each instance a statement shall be entered in the individual's medical record indicating the work-unit number and title, and a notation of the physical and/or psychological effect, or lack of same, resulting from the investigation.

UNITED STATES GOVERNMENT

Memorandum

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE

TO : See list below

DATE: October 30, 1967

FROM : Surgeon General William H Stewart

SUBJECT: PHS policy for intramural programs and for contracts when investigations involving human subjects are included

I. Introduction

Advances in health depend on the creation of new knowledge. The Public Health Service conducts and supports research in medicine, in the health sciences and in the sciences related to health to obtain this knowledge. Some of this research can be done in the test tube and laboratory animals, but man himself is the ultimate necessary subject of study in the clinical phases of medical research, in most social and behavioral research and in epidemiologic and other public health research. The use of human beings as subjects in research poses problems for the investigator and his institution. The principles which follow reflect the present position of the Public Health Service and apply to intramural programs and to contracts (a statement of policy applicable to extramural programs was issued in PHS Policy and Procedure Order No. 129, revised July 1, 1966, supplemented December 12, 1966, and January 24, 1967).

Each Bureau Director*, having responsibility for intramural programs and for contracts, shall file with the Surgeon General a description of the policy and procedure that his Bureau will follow in adhering to these principles. The Bureau Director shall report to the Surgeon General all subsequent changes in this policy and procedure.

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*Reference is to all Directors who report directly to the Surgeon General, e.g., those of the Office of Comprehensive Health Planning and Development, OSG, the National Center for Health Statistics, and the National Library of Medicine.

Addressees:

Director, Office of Comprehensive Health Planning and Development, OSG
Director, Bureau of Disease Prevention and Environmental Control
Director, Bureau of Health Manpower
Director, Bureau of Health Services
Director, National Center for Health Statistics
Director, National Institute of Mental Health
Director, National Institutes of Health
Director, National Library of Medicine
Assistant General Counsel (Public Health Division)

II. Intramural Programs

A. The Subject.

The welfare of the individual is paramount.

1. Health and Safety.

a. The subject must have available to him the facilities and professional attention necessary for the protection of his health and safety.

b. The health and safety of persons other than the subject, if endangered by the research procedures, must be protected.

2. Rights.

a. Respect for the subject's privacy, dignity, comfort and legal rights is essential.

b. The individual must be free to make his own choice whether to be a subject in research. His participation shall be accepted only after he has received an explanation of the procedures, benefits, hazards and discomforts, and, suited to his comprehension, of the reasons for the study and its general objectives. He must be informed of his right to withdraw from the study at any time. An explanation so detailed as to bias his response or otherwise to invalidate findings is not necessary in those behavioral, social, epidemiologic and demographic procedures that involve no risk of harm to the subject.

c. The considerations that relate to the particular situations in which the subject's fully informed consent may not be desirable or necessary are described in Sections IIE1, 4, 5 and 6, below.

B. The Research.

1. Excellent clinical and other research in man is to be encouraged. Achievement of excellence requires sound and creative scientific design which incorporates effective measures for ensuring that the potential benefits to the subjects and the importance of the knowledge to be gained outweigh the inherent risks to the health, safety, comfort and rights of the subjects. Investigations shall be designed to preclude nondiagnostic or nontherapeutic procedures with inherent likelihood of death or of serious or permanent mental or physical impairment of the subjects.

2. Major Categories of Subjects in Research.

a. Patients: Individuals who come to a physician or dentist for advice and care.

Studies with patients may be classified as:

(1) Diagnostic, therapeutic, or preventive in intent, which help the physician or dentist to understand and take care of the patient or to understand and take care of his relatives when it is appropriate to investigate the familial nature of a disease

(2) Designed to elucidate basic mechanisms of the patient's disease process but not resulting in direct or early benefit to the patient

(3) Not intended for the direct benefit of the patient and not directly related to his disease (the patient in such a study serves in a role similar to that of a normal volunteer).

b. Normal Volunteers: Individuals without known significant disease who have volunteered to participate in research in a clinical setting (hospital, clinic or other place where patients receive medical or dental treatment) or to participate in evaluative studies designed to improve the health of the public (e.g., studies of vaccine development or nutrition).

c. Other Research Subjects: Individuals who participate in studies not conducted in a clinical environment (examples include certain studies in the behavioral and social sciences, epidemiology and demography).

C. Review and Approval.

1. All proposed investigations shall be reviewed, for adherence to the above principles, by other than those directly involved in the conduct of the research. The depth of review and the administrative level of consideration and approval must be commensurate with the character of the research and with the magnitude of the benefits and hazards to the subjects.

Examples of appropriate levels of review and approval for several broad categories of clinical and other research including human subjects are set forth in Section IIE, below. In general, the

approval of a project involving a normal volunteer or of a project involving a patient when the project is not intended for his benefit shall be at the level of the Bureau Director.

2. The review of proposed investigations shall include group consideration of the following:

   a. The scientific merit of the proposal, including its research design and the importance of the knowledge to be gained

   b. The qualifications of the responsible investigator (defined below) and the adequacy of facilities and other resources for both the work to be done and the protection of the subjects

   c. The risks to the subjects

   d. The adequacy of the procedures for securing informed consent from the subjects

   e. The adequacy of measures for the protection of the health, safety, comfort and rights of the subjects.

3. The review, by committee, specialized panel or other group structure, must assure that the judgments about the investigator and his proposal are determined by several persons and are objective, competent and valid.

4. Significant changes in protocol and emergent problems of investigation, particularly changes or problems that may affect the health, safety, comfort or rights of the subjects, shall be brought to the attention of the review group involved.

D. Responsibility.

1. The immediate responsibility for the welfare of human subjects in research rests with the person in charge of the design and conduct of the research (responsible investigator).

   a. The purely medical or dental aspects of a research project shall be under the supervision of physicians or dentists who are specifically, rather than generally, qualified to assume responsibility for the health of the subjects. It is the responsible investigator or his designee who must inform the subjects about the project and seek their informed consent to participate. He must take effective action when significant pathology is observed during an investigation,

regardless of the relationship of the pathology to the investigation. Illustrative of such action is treatment, if the investigator is the appropriate and qualified therapist, or notification of the patient or his physician or dentist.

b. The responsible investigator must be qualified to conduct his project. These qualifications must be examined in detail; special training and experience may be more important than formal credentials.

c. A PHS employee, detailed to a non-PHS organization where he is responsible for an investigation involving human subjects, shall comply with PHS policy to the extent this policy does not conflict with that of the sponsoring organization. He must, however, assure that the procedures of his investigation reflect standards of ethics and of other concern for the individual that are no less rigorous than those of the PHS. (Section III, below, states the relevant PHS policy for contracts, and PHS PPO #129, revised, for grants.)

2. The Bureau Director or his designee is responsible for determining the particular mode of group review, for selecting the membership of the group, and for acting on the group's recommendations for approval, disapproval or modification of proposals.

3. Existing lines of authority within the Bureau shall be used to assure adherence to these principles and to assure effective communication between review groups and investigators.

4. Written records shall be maintained of the review and of other deliberations of the groups appointed for the review.

E. Special Considerations.

1. Research consisting of observations made during the administration of accepted health care procedures may require no more than review in discussion by the investigator responsible for the project with colleagues, including supervisory personnel not personally involved in the study. Ward rounds, conferences, or staff meetings provide appropriate occasions for this type of review. The need to obtain informed consent is determined by the specific procedures involved in routine practice; consent is often not required for observational research.

2. Research deviating from accepted medical or dental practice (certain studies referred to in Section IIB2a(1)) shall be given more formal group consideration as specified by the Bureau Director. The responsible investigator shall record the patient's informed consent in the medical or dental record.

3. Research involving normal volunteers (Section IIB2b) and patients who are serving in a similar role (Sections IIB2a (2) and (3)) shall be reviewed by a group established in accordance with Section IIC. The final decision is to be made by the Bureau Director or his designee. Written informed consent is preferable in all cases and is mandatory for all projects involving normal volunteers.

4. The review of research in the social and behavioral sciences and in epidemiology, demography and related disciplines involves additional special considerations. Separate groups may be designated to assure competence and independence of review for particular areas.

   In much of such research there is no personal risk to the subject, and the issues of concern are the fully voluntary nature of the participation of the subject, the maintenance of confidentiality of information obtained from the subject, and the protection of the subject from misuse of the findings. For example, a major class of procedures in the social and behavioral sciences does no more than observe or elicit information about the subject's status by means of tests, inventories, questionnaires or surveys of personality or background. In such instances, the ethical considerations of voluntary participation, confidentiality and propriety in use of the findings are the most generally relevant ones. The procedures may in many instances not require the fully informed consent of the subject or even his knowledgeable participation. In such instances full documentation is necessary for the record.

   Some investigations in the social and behavioral sciences involve procedures designed to alter the status of the individual, as, for example, studies of human learning, social perception or group effectiveness. In such research the effects, if any, on the subject may be transitory or enduring but must be carefully assessed for their possible harmfulness.

5. Whatever the nature of the investigation, the concern for the protection of the subject and for the assurance of voluntary participation is essential and becomes most critical when the subject is not of age or competence to make an adequate judgment

in his own behalf. Studies involving children, the mentally ill or the mentally defective shall be carried out only when there is no significant risk of physical or mental harm to the subject or when direct benefit to the subject is anticipated. The specific issues shall be considered by a review group, as specified by the Bureau Director or his designee. In general, written informed consent of the parent or guardian shall be required for all medical or dental studies with such subjects, except in studies of an observational nature or in those conducted during the administration of accepted health care procedures that do not require specific informed consent in ordinary practice. Any exceptions shall be carefully considered and fully documented. Written informed consent of parent or guardian may be desirable in certain other studies with these groups and shall be required if conditions warrant.

6. Studies of individuals with limited civil freedom shall also be subject to group consideration and approval as specified by the Bureau Director or his designee. Informed consent of the responsible authority shall be required in all cases. Written informed consent of the individual shall also be required except for studies of an observational nature, conducted during the administration of accepted health care procedures that do not require specific informed consent in ordinary practice.

III. Procedures for Contracts

A. Any research contract likely to require the use of human subjects in carrying out the contract shall be reviewed, prior to final approval, by an appropriate group (see Section IIC) to determine the performer's capability for meeting his responsibility to protect the rights and welfare of the research subjects. The contract shall contain provisions making clear that the performer is responsible for protecting the rights and welfare of the research subjects and for conducting the work carefully and prudently.

B. If the prospective performer is a grantee who has given and has had approved by the PHS an assurance in accordance with PPO #129, revised, relating to investigations involving human subjects, the contract shall require that the work be conducted in accordance with that assurance.

C. If an institution-wide assurance has not been given or approved, the contract shall contain provisions requiring:

1. The submission, subject to approval by a research review group established by the initiating bureau in accordance with Section II, of a protocol, supplemented with full information about the qualifications of the investigators and the facilities to be made available both to conduct the work and to protect the subjects.

2. The specification of measures otherwise to secure adherence to the principles in Section II.

AMES MANAGEMENT MANUAL

TRANSMITTAL SHEET NO. 89

Jan 15, 1968

- MATERIAL TRANSMITTED

AMM 7170-1, Human Research Planning and Approval, sets forth general policy and procedures for the planning and approval of research involving human subjects.

- FILING INSTRUCTIONS

Insert the attached in the NASA-Ames Management Manual.

Arthur B. Freeman
Assistant Director for Administration

Reed 1/15/68

AMES RESEARCH CENTER

AMM 7170-1

MANAGEMENT MANUAL

SECTION PROGRAM FORMULATION

SUBJECT Human Research Planning and Approval

1. PURPOSE

This article sets forth general policy and procedures for the planning and approval of research involving human subjects.

2. APPLICABILITY

This article applies to all human research conducted for or on behalf of Ames Research Center by:

a. Any officer or employee of the United States or any other person, entity, or institution.

b. Any NASA contractor, subcontractor (at any tier), or grantee, to the extent that this article is incorporated, by reference or otherwise, in the relevant contract, subcontract, or grant.

3. AUTHORITY

Section 203(b)(1) of the National Aeronautics and Space Act of 1958 as amended, 42 U.S.C. 2473(b)(1).

4. DEFINITION: "HUMAN RESEARCH"

Notwithstanding other technical usage, the term "Human Research," for purposes of this article, means any test, experiment, or other evaluation procedure in the course of which, or as a result of which, a human subject may be exposed to conditions which could reasonably be expected to cause distress, pain, impairment of health, physical injury, personality or emotional disorder, or death.

5. RIGHTS OF SUBJECTS

Apart from the obtaining of a proposed subject's consent in accordance with paragraph 8, no subject shall be asked to waive any rights that may arise in connection with any injury, loss, or death suffered by the subject

as a result of human research.

6. GENERAL PROCEDURAL REQUIREMENTS FOR HUMAN RESEARCH: WAIVERS

a. Except as provided in subparagraph 6b, all human research within the scope of this article shall be conducted only in accordance with the procedures set forth in paragraphs 7 through 12.

b. In some instances of human research, the requirements set forth in this article may, for various reasons, not be necessary to protect the subject of such human research. In such instances, upon the request of the principal investigator, the Director may, at his discretion, waive some, or all, of the requirements contained in this article. Moreover, the Director may, at his discretion, categorically waive the requirements of this article, in whole or in part, with respect to classes of trained persons who knowingly follow a specialized calling or occupation which is generally recognized as hazardous including, by way of description but not limitation, the callings of test pilots and astronauts. Nothing contained herein, however, shall be construed as authorizing the use or employment of any person for any purpose if there exists a likelihood that such employment will result in serious or permanent injury or death.

7. EXAMINATION OF SUBJECTS BY PHYSICIANS

a. No human research shall be conducted unless a physician, having been informed of the nature of the proposed human research, finds the subject medically qualified therefor. Such finding shall be based upon an examination of a nature and scope believed by the physician to be reasonable under the circumstances.

b. At the conclusion of the human research, the subject shall be re-examined by a physician.

c. A report of the results of such examination and re-examination shall be promptly forwarded to the Director.

8. VOLUNTARY INFORMED CONSENT

a. Except as provided in subparagraph 8b:

(1) No human research may be conducted unless the subject voluntarily agrees to participate in the human research, has freely

given his informed consent in accordance with this subparagraph 8a. and has the legal capacity to so consent.

(2) No consent given by a subject shall be deemed informed unless, prior to the giving of consent, the proposed human research is explained to the subject in language understandable to him. Such explanation must include the nature, duration, and purpose of the human research; the manner in which it will be conducted; and all foreseeable risks, inconveniences, and discomforts to the subject that might result from the conduct of the human research. If the nature of such risks, inconveniences, or discomforts is not known, this fact must be made known to the subject. In addition, the subject must be informed that he may withdraw from the human research at any time, or if this is not in fact the case (because the circumstances of the experiment make such withdrawal unwise, dangerous, or impossible), he must be so advised.

(3) A subject must give his consent in writing in such form as will indicate that he has been fully informed of, and voluntarily accepts, the risks, inconveniences, and discomforts which may be involved.

(4) A person who is a minor or who is without legal capacity to give his voluntary informed consent shall not be a subject of human research without specific authorization in writing signed by the NASA Administrator.

b. The Director may waive some or all of the requirements of subparagraph 8a if he determines that, due to the requirements of the proposed human research (e. g., necessity that the subject be unaware that he is participating in an experiment; nature of experiment requires use of minors when otherwise authorized), such research would be seriously hampered by any of the requirements of subparagraph 8a.

9. PROTOCOLS: AUTHORIZATION OF HUMAN RESEARCH BY THE DIRECTOR

a. No human research within the scope of this article may be conducted unless:

(1) The principal investigator has submitted to the Director a protocol prepared in accordance with Attachment A.

(2) The Director, after considering the protocol of the principal investigator, authorizes the human research.

b. In determining whether the proposed human research should be authorized,

AMES RESEARCH CENTER

AMM 7170-1

MANAGEMENT MANUAL

SECTION PROGRAM FORMULATION

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Notwithstanding other technical usage, the term "Human Research," for purposes of this article, means any test, experiment, or other evaluation procedure in the course of which, or as a result of which, a human subject may be exposed to conditions which could reasonably be expected to cause distress, pain, impairment of health, physical injury, personality or emotional disorder, or death.

5. RIGHTS OF SUBJECTS

Apart from the obtaining of a proposed subject's consent in accordance with paragraph 8, no subject shall be asked to waive any rights that may arise in connection with any injury, loss, or death suffered by the subject

as a result of human research.

6. GENERAL PROCEDURAL REQUIREMENTS FOR HUMAN RESEARCH: WAIVERS

a. Except as provided in subparagraph 6b, all human research within the scope of this article shall be conducted only in accordance with the procedures set forth in paragraphs 7 through 12.

b. In some instances of human research, the requirements set forth in this article may, for various reasons, not be necessary to protect the subject of such human research. In such instances, upon the request of the principal investigator, the Director may, at his discretion, waive some, or all, of the requirements contained in this article. Moreover, the Director may, at his discretion, categorically waive the requirements of this article, in whole or in part, with respect to classes of trained persons who knowingly follow a specialized calling or occupation which is generally recognized as hazardous including, by way of description but not limitation, the callings of test pilots and astronauts. Nothing contained herein, however, shall be construed as authorizing the use or employment of any person for any purpose if there exists a likelihood that such employment will result in serious or permanent injury or death.

7. EXAMINATION OF SUBJECTS BY PHYSICIANS

a. No human research shall be conducted unless a physician, having been informed of the nature of the proposed human research, finds the subject medically qualified therefor. Such finding shall be based upon an examination of a nature and scope believed by the physician to be reasonable under the circumstances.

b. At the conclusion of the human research, the subject shall be re-examined by a physician.

c. A report of the results of such examination and re-examination shall be promptly forwarded to the Director.

8. VOLUNTARY INFORMED CONSENT

a. Except as provided in subparagraph 8b:

(1) No human research may be conducted unless the subject voluntarily agrees to participate in the human research, has freely

the Director will consider, among other things, whether:

(1) The importance of the objective of the research outweighs the inherent risks to the subject.

(2) The subject of the human research will be unnecessarily exposed to risk of injury, discomfort, or inconvenience.

(3) The subject or his representatives will receive adequate compensation, by reason of insurance, workman's compensation, or the like, in the event the subject suffers any loss, injury, or death as a result of the human research.

10. ADVISORY BOARDS

The Director may, at his discretion, appoint a board to advise him as to matters within the scope of this article.

11. LEGAL AND MEDICAL REVIEW

A copy of the protocol to be submitted to the Director in accordance with paragraph 9, or waiver requests submitted pursuant to paragraphs 6 and 8b, shall be submitted through the Chief Counsel and the Chief, Medical Office.

12. REPORTS OF INJURIES AND CHANGES IN PROCEDURES

The principal investigator of human research within the scope of the article shall immediately inform the Director in the event of:

a. Any injury to a subject.

b. Any deviation from the procedures set forth in the protocol submitted pursuant to paragraph 9.

13. DISTRIBUTION
ADSL-10

H. Julian Allen
Director

AMM 7170-1
ATTACHMENT A

The protocol to be submitted to the Director in accordance with paragraph 9 shall provide the following information:

1. The title of the proposed research.
2. Name of organization conducting the research or for which the research is being conducted.
3. Name and qualifications of principal investigator (and of co-investigators, if any).
4. Name and qualifications of persons who will conduct the human research (unless covered in item 3).
5. The purpose of the research, including an explanation of why the use of human subjects is required.
6. The plan of study.
7. Historical background of the research, with references to pertinent scientific literature. This should include a discussion of relevant prior research using humans and/or animals.
8. Proposed safety precautions.
9. Expected duration of the study. (Give approximate beginning and ending dates.)
10. Expected number of subjects to be used.
11. The source from which subjects are expected to be obtained.
12. Criteria to be used in selecting subjects.
13. Possible inconveniences, discomforts, pain, and risks to the subject the research may present.
14. Will the subject be free to withdraw from the research at any time? If not, when and why.
15. Wage, salary, or other payment, if any, to be paid to the subject.

AMM 7170-1
ATTACHMENT A

16. Source (Federal or state compensation acts, insurance, other) and general description (include examples of dollar amounts) of compensation, if any, to be received by a subject or his representatives in the event of injury.

17. Availability of a physician during the research. (Indicate whether a physician will be present at all times; if not, the location of the nearest physician(s) during the performance of the research.)

18. What information concerning the human research is intended to be communicated to the subject. (Include information to be communicated to the subject in the course of obtaining his consent. See paragraph 8 of the article.)

19. The proposed form of consent the subject will be asked to execute.

20. If a determination pursuant to paragraph 6b or 8b has been, or will be, requested, the protocol should so indicate.

DISPOSITION FORM

(AR 340-15)

REFERENCE OR OFFICE SYMBOL	SUBJECT
CRDLS	Research Use of Human Subjects

TO TSG
ATTN: Spec Asst for R&D

FROM CRD

DATE 6 Jan 69

CMT 1

COL Ley/43331

1. The staff study attached as Inclosure 1, subject: Review of Department of the Army Policy on Use of Human Subjects in Research, dated 7 January 1969, is forwarded for information and comment.

2. This study was prepared by COL H. L. Ley, Jr., MC, during ACDUTRA after review of both ARO and AMEDD files on this subject, and discussions with COLS Plough and Rosenberger of your Command.

3. I am in agreement with the Conclusions of the study, and consider that it is desirable for AMEDD to initiate minor changes in review procedures for research projects involving the use of human subjects. Your specific recommendations are requested regarding the following points:

a. Which of the three possible courses of action outlined in para 5b of the study is considered most desirable?

b. Would you recommend the change in approval authority for use of radioisotopes presented in para 5f of the study?

c. Would you consider the Contract Review Board, appropriately renamed, a satisfactory instrument for medical-legal review of all research involving human subjects to insure that appropriate consideration is given to the rights of the individual?

FOR THE CHIEF OF RESEARCH AND DEVELOPMENT:

/s/

1 Incl
Staff Study

DONALD L. HOWIE
Colonel, GS
Chief, Life Sciences Division

DA FORM 2496 REPLACES DD FORM 95, EXISTING SUPPLIES OF WHICH WILL BE ISSUED AND USED UNTIL 1 FEB 63 UNLESS SOONER EXHAUSTED. U.S. GOVERNMENT PRINTING OFFICE : 1933 O—73.

CRDLS 8 January 1969

MEMORANDUM FOR: COLONEL HOWIE

SUBJECT: Report of ACDUTRA

1. A Staff Study, subject: Review of Department of the Army Policy on Use of Human Subjects in Research, dated 7 January 1969, is submitted as a report of ACDUTRA for the undersigned, see Inclosure 1.

2. The study contains two recommended actions, one of which can be initiated immediately and the second after completion of the first.

3. It has been a pleasure to work on this problem, which I believe is an excellent example of the kind of study well suited to Mob Des appointees. Your staff, professional and secretaries alike, have been most helpful in making it possible to complete the study in the two week period of duty.

HERBERT L. LEY, Jr.
Colonel, MC

1 Incl
Staff Study

7 January 1969

SUBJECT: Review of Department of the Army Policy on Use of Human Subjects in Research

1. PROBLEM. To review present Department of the Army (DA) policy on unclassified research projects involving use of human subjects to identify potential problem areas that DA should consider in further evolution of its policy.

2. ASSUMPTIONS.

a. The present climate of public opinion regarding the use of human subjects in research will continue for the foreseeable future.

b. Based on current reviews by the Public Health Service (PHS) regarding use of human subjects in medical investigations, it is assumed that PHS will publish a revised policy in the near future which will require a more formalized review of research applications submitted by civilian medical institutions to the PHS.

3. FACTS BEARING ON THE PROBLEM.

a. The present climate of public opinion regarding the use of human subjects for research reflects strong and serious concern for the rights of the individual in the experimental situation. This concern is based on the revelations of the Nuremberg Trials and the publicity given to the subject by Dr. Henry K. Beecher in his article in the New England Journal of Medicine of 16 June 1966. This climate has led in recent years to the Food and Drug Administration (FDA) regulation on "Informed Consent," the World Medical Association's, "Declaration of Helsinki," and the American Medical Association's "Ethical Guidelines for Clinical Investigation."

b. If the PHS policy is made more restrictive, this action will bring moral pressure on DA to review its procedures for the use of human subjects in medical investigations to insure that these procedures are consistent with the spirit of the revised PHS policy.

c. Current DA policy is outlined in the following three Army regulations:

(1) AR 70-25, Use of Volunteers as Subjects of Research, dated 26 Mar 62, see Annex A.

(2) AR 40-7, Clinical Use of Investigational Drugs, dated 21 Jul 67, see Annex B.

(3) AR 40-37, Radioisotope License Program (Human Use) dated 16 Aug 63, see Annex G.

d. Current requirements for review and approval authority for use of volunteers or patients for experimental investigations vary with the sponsorship of the project and other factors. A tabular summary of the current DA review and approval procedures, based on the AR's listed in para 3a is attached as Annex D. Depending upon the nature of the investigation the application may be reviewed by the Army Investigational Drug Review Board (AIDRB), the Preventive Medicine Division (PMD) of The Office of The Surgeon General (OTSG) and the Medical Research and Development Command (MRDC).

e. The Directorate of Professional Services (DPS), OTSG, may also review and approve use of investigational drugs in emergency treatment situations.

4. DISCUSSION.

a. Over the six years that have elapsed since publication of AR 70-25, DA policy on the use of volunteers has been commendable. A comparison of DA and PHS policies over this period reflects most favorably on DA because it formalized in AR 70-25, at an early stage following the 1961 amendments of the Food Drug and Cosmetic Act (FDCA), a policy of review of use of volunteers as subjects of research that was not paralleled by PHS in its grant program until 1966. This fact is perhaps a result of the extensive experience of DA with volunteer studies over the past 25 years and the serious consideration given over the entire period to the rights of the individual in such studies.

b. Present MRDC policy regarding review of research contracts and grants utilizing volunteers or patients as subjects of research varies considerably with the specialty area concerned. For research projects under review by the Armed Forces Epidemiological Board (AFEB) and its Commissions, intensive two-level review occurs with strong emphasis placed on ethical considerations. Furthermore, the AFEB review process makes a matter of record the details of such reviews. Although all MRDC contracts dealing wit human subjects contain a special article outlining policy of The Surgeon General (TSG) regarding use of human volunteers, see Annex E, it appears that often no formalized review of record is made of contract applications in the non-AFEB area to insure that this policy is followed by the contracto

c. Investigational drug studies represent a special area of activity of Army Medical Department (AMEDD). The AIDRB, under AR 40-7, has principal responsibility for this area. FDA does not routinely approve industry-sponsored drug studies prior to their initiation by industry, a fact that should be weighed by AIDRB in considering studies from that source. A legal

distinction should also be drawn in emergency treatment situations between therapeutic use of a marketed drug for an indication other than that for which the drug is labeled and use of a non-approved drug. These two situations place quite different levels of review responsibility on TSG and may for that reason probably require separate treatment by the AIDRB.

d. Drug studies with radioactive drugs are a special situation which is unique in that AR 70-25 and AR 40-37 specify that Secretary of the Army (SA) approval is required for any research with nuclear agents using volunteers. This restriction appears appropriate for studies of medical hazards of fallout materials or radiation from nuclear devices. However, the medical use of radioisotopes in patients for both diagnostic and therapeutic purposes is so common at this time that it appears logical to exempt it from specific approval by either SA or the Chief of Research and Development (CRD). This exemption is permitted under para 3c, AR 70-25. Similarly, the use of tagged investigational drugs is common in metabolic studies of investigational drugs sponsored by industry. The FDA policy is to consider tagged analogues of investigational drugs as comparable to the investigational drug itself. If DA were to follow this FDA policy, approval of the use of tagged investigational drugs in patients by the AIDRB and EHD, OTSG, should provide adequate review for such use. If such studies were performed in volunteers, approval by CRD would be appropriate. These procedures appear to be the intent of Memorandum for Record by LTC T. R. Ostrom, Subject: Approval for Requests for Use of Human Volunteers in Research, dated 1 Dec 65, see Annex F, and COL D. L. Howie's Memorandum for the Director of Army Research, Subject: AR 70-25, Use of Volunteers as Subjects of Research, dated 11 Jun 68, see Annex G. An earlier policy statement in a Disposition Form to TSG from CRD, Subject: AR 70-25, dated 25 May 64, see Annex H, appears to be at variance with later documents in para 3b in stating "It is the policy of this office to seek the approval of the Secretary of the Army for all research wherein human volunteer subjects are exposed to ionizing radiation from any type of source." Such a policy seems unnecessarily restrictive considering the wide-spread use of tagged investigational drugs in medical research today.

e. The use of investigational drugs in emergency treatment situations poses minor problems in identifying the group within OTSG responsible for approval of such uses. As noted in para 4c above, a legal distinction exists between marketed drugs used for new indications and non-marketed, non-approved drugs used for similar indications. In the first case, provided the drug is purchased in the marketplace and not provided by the manufacturer to the physician, the use of the drug by the physician for indications other than those for which the drug is labeled is considered within the realm of medical practice. The physician may embark on such uses on his own responsibility, guided by his professional knowledge and information available in the public domain concerning side effects, contraindications and adverse reactions. For such use of a drug approval by the DPS, OTSG, would be highly appropriate. For a drug not yet approved for marketing

emergency use is considered investigational use by the FDA, and under these conditions, approval of use by AIDRB would be consistent with the policy of requiring approval of other investigational drug studies by AIDRB.

f. The subject of investigational controls for studies of new medical devices in man is in a state of flux at this time. A recent court decision held that devices were subject to the FDCA (AMP Decision). An appeal of this decision was declined by the US Supreme Court. If the decision continues to be upheld by the courts, devices are subject to the same investigational controls as are drugs. FDA is not inclined to move rashly into this area, but may approach certain cases on a test case basis, e.g., intra-uterine devices. It is important for AMEDD to remain current in this area.

g. A review of AR's 70-25, 40-7 and 40-37 raises the question whether these three regulations could be integrated into a single regulation. This is an attractive possibility, particularly if such a combined regulation might be adopted as a DOD instruction.

5. CONCLUSIONS.

a. AR 70-25 is basically a sound approach to DA use of volunteers as subjects of research, fully in accord with PHS and FDA policy in the same area.

b. PHS policy changes concerning use of human subjects in research that are currently being discussed will, if implemented, place increased pressure on DA either to follow the pattern that PHS requires or to develop a different pattern better suited to DA. In either case, DA should insure that all use of human subjects, both volunteer and patient, in research be subjected to a medical-legal review to confirm that such investigations are conducted in accord with the highest ethical standards to protect the rights of the individual subject. There are three courses of action to consider as follows:

(1) The first approach would be to accept the new PHS policy and to require that all sponsoring institutions of contract and grant applications define their review process, create a review committee of appropriate membership, and periodically review all work conducted with human subjects in the institution. This approach would require the review of all AMEDD intramural research involving human subjects by an AMEDD or MRDC committee.

(2) The second approach would be not to accept the PHS approach but to review all research involving human subjects, whether extramural or intramural, by an AMEDD or MRDC committee.

(3) The third approach would be to move initially as outlined in para 5b(2) and to supplement this with the procedure of para 5b(1) within

a year or two after the new PHS requirements are accepted by the scientific and medical communities.

c. AR 40-7 should be reviewed for possible revision in the following areas:

(1) A clearer delineation of the respective responsibilities of MRDC, AIDRB, PMD and DPA in the review and approval of investigational drug studies.

(2) A decision whether the thrust of this regulation is "investigations" or "investigational drug studies."

(3) A delineation of the approval authority for investigational studies of marketed vs. non-approved drugs.

(4) A reevaluation of the approval requirements of Phase I and II vs. Phase III drug studies, considering that FDA does not approve such studies before they are initiated and that the former involve significantly greater hazard than the latter.

d. AMEDD should be aware of recent legal decisions supporting the position that medical devices fall under the provisions of the FDCA. Consideration should be given, as policy evolves in this area, to reviewing research investigations involving human subjects and new devices under guidelines similar to those now employed with drugs. The position can also be taken that, irrespective of the legal question, all research studies using human subjects, whether involving drugs or devices, should meet the same criteria of ethical propriety.

e. Consideration should be given at a later date to consolidation of AR's 70-25, 40-7, and 40-37 and to proposing such a consolidated regulation for DOD issuance.

f. Consideration should be given to formally revising CRD policy regarding approval authority for use of radioisotopes as follows:

(1) That all studies in volunteers of hazards of by products or radiation of military nuclear devices or energy sources be referred to the Secretary of the Army for approval.

(2) That all other studies involving use of radioisotopes in <u>volunteers</u> be referred to CRD for approval.

(3) That all other studies involving use of radioisotopes in <u>patients</u> be referred to TSG for approval.

6. ACTION RECOMMENDED.

a. That the DF attached as Annex I be signed to transmit this study to AMEDD for information and comment, particularly in regard to the choice of options listed in para 5b.

b. That following receipt of comments from AMEDD, this report and their comments be reviewed to prepare a position paper recommending change of DA policy regarding approval of radioisotope studies in man as outlined in para 4d.

/S/

9 Incl
as

HERBERT L. LEY, JR.
Colonel, MC

E

Article_____The following enumerated Principles, Policies and Rules of The Surgeon General, Department of the Army, relating to the use of Human Volunteers in Medical Research are incorporated in and made a part of this contract:

1. The voluntary consent of the human subject is essential. This means that the person concerned:

a. Should have legal capacity to give consent.

b. Should be so situated as to be able to exercise free power of choice, without intervention of force, fraud, deceit, duress, over-reaching, or other form of constraint or coercion.

c. Should have sufficient knowledge and understanding of the experiment to enable him to make an enlightened decision, on the basis of explanation given to him as specified below:

d. Should state his consent in writing, signed in the presence of at least one witness who shall attest to such signature in writing.

2. Each individual who initiates, directs or engages in the experiment has a personal duty and responsibility for ascertaining the quality of the volunteer's consent.

3. Before the acceptance of consent of the volunteer, he must be given adequate explanation. He should be informed of the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonably to be expected; and the effects upon his health or person which may possibly come from his participation in the experiment.

4. The experiment should be such as to yield fruitful results for the good of society, unprocurable by other means of study, and not random and unnecessary in nature.

5. The number of volunteers used must be kept at a minimum consistent with the requirement of a fruitful experiment for the good of society.

6. In order that the anticipated results will justify doing the experiment, it (the experiment) should be designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problem under study.

7. The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury.

8. No experiment should be conducted where there is a prior reason to believe that death or disabling injury will occur.

9. The degree of risk to the volunteer should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.

10. The experiment should be conducted only by scientifically qualified persons (including an adequately trained physician) who shall be required to exercise the highest degree of skill and care throughout the experiment. Competent consultants should be available on short notice in this connection.

11. Adequate preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability or death. This includes hospitalization and medical treatment as may be required.

12. The human volunteer subject should be at liberty to bring the experiment to an end if he feels that it is impossible for him to continue under the test.

13. The scientist or physician in charge must be prepared to terminate the experiment at any stage, if he has probable cause to believe, in the exercise of the good faith, superior skill and careful judgment required of him that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject.

14. Established policy prohibits the use of prisoners of war in human experimentation. They will not be used under any circumstances.

15. Agents used in research must have the following limiting characteristics:

a. Controllable lethality

b. No serious chronicity anticipated

c. Effective therapy available

d. Adequate background of animal experimentation.

F

CRD/N 1 December 1965

MEMORANDUM FOR RECORD

SUBJECT: Approval for Requests for Use of Human Volunteers in Research

1. References:

a. AR 70-25

b. Telephone call, 29 Nov 65, from Lt Col Frank Taylor, GS, XO, DAR, to undersigned.

c. Meeting, 30 Nov 65, with Lt Col Taylor, Lt Col W. F. Williams, Asst Exec, OCRD, and undersigned.

2. By ref 1b, the question was raised as to the authority of Chief, Life Sciences Division, to sign "For the Chief of Research and Development" in certain cases involving use of human volunteers in research. The question had arisen in the Office of the Executive, OCRD, during review of the reading file and involved human volunteers in medical research.

3. Ref 1a, paragraph 6, states that "The Surgeon General will review the proposal and forward it with his comments and recommendations on medical aspects to the Chief of Research and Development for approval." Paragraph 6 further indicates that cases involving nuclear chemical or biological (NCB) experiments require Secretary of Army approval. Discussions with Chief, Life Sciences Division, revealed that in the development of the human volunteer program in the period 1955-1956, the authority to sign "For the CRD" was delegated to Chief, Life Sciences Division, in all cases except NCB. A search of the files did not uncover written authority. However, in view of the system of file retirement this is not considered unusual.

4. By ref 1c, the material contained in para 3 was discussed. It was agreed that the present procedures would be followed in all cases with the exception of the following modification. The Chief, Life Sciences Division, will continue to sign "For the CRD" all approvals for use of human volunteers with the exception of NCB cases. Where the Chief, Life Sciences Div, signs, the approval will be routed through CRD and the routing slip will be marked "For Information Prior to Dispatch."

5. A copy of this memorandum should be permanently maintained in the "Human Volunteers" files.

THOMAS R. OSTROM
Lt Colonel, GS
Life Sciences Division

Encl 7

Source of Application	Sponsor	Testing	Man	Field Review	Initial HQ Review	Coordination	Tech Approval Authority	Tech Approval Authority
DA (Res)	DA	Stress	S	USAMRU	MRDC	None	TSG	CRD
" "	"	Drug Ph I	S	USAMRU	MRDC	DRB	TSG	CRD
" "	"	Drug* Ph I	S	USAMRU	MRDC	DRB, PMD	TSG	CRD - SA
" "	"	Drug Ph III	P	USAMRU	MRDC	DRB	TSG	TSG
" "	"	Drug Ph IV	P	USAMRU	MRDC	DRB, CONARC	TSG	Varies
DA (Clin)	DA	Stress	P	Hosp	NA	NA	NA	NA
" "	"	Drug Ph I	S	Hosp	DRB	None	TSG	CRD
" "	"	Drug* Ph I	S	Hosp	DRB	PMD	TSG	TSG-SA
" "	"	Drug Ph III	P	Hosp	DRB	None	TSG	TSG
DA (Clin)	Industry	Drug Ph I	S	Hosp	DRB	None	TSG	CRD
" "	"	Drug* Ph I	S	Hosp	DRB	PMD	TSG	CRD-SA
" "	"	Drug Ph II	P	Hosp	DRB	None	TSG	TSG
" "	"	Drug Ph III	P	Hosp	DRB	None	TSG	TSG
Civ (Contract)	Civ Inst	Stress	S	Civ Inst	MRDC	None	TSG	CRD
" "	" "	Drug Ph I	S	Civ Inst	MRDC	DRB	TSG	CRD
" "	" "	Drug* Ph I	S	Civ Inst	MRDC	DRB, PMD	TSG	CRD-SA
" "	" "	Drug Ph II	P	Civ Inst	MRDC	DRB	TSG	TSG
" "	" "	Drug Ph III	P	Civ Inst	MRDC	DRB	TSG	TSG

Key:
Man, S indicates Subject; P indicates Patient
USAMRU, a generic term for an Army medical research unit
MRDC, US Army Medical Research and Development Command
DRB, Army Investigational Drug Review Board
PMD, Preventive Medicine Division, Office of The Surgeon General
SA, Secretary of the Army
Civ Inst, Civilian institution
* indicates radioactive drug

G

CRDLS 11 June 1968

MEMORANDUM FOR: DIRECTOR OF ARMY RESEARCH

SUBJECT: AR 70-25 "Use of Volunteers as Subjects of Research"

1. The undersigned has, in the past, assumed the responsibility for approving Army sponsored research proposals for the Chief of Research and Development under the following criteria:

a. No. NBC agents are involved.

b. All provisions of AR 70-25 concerning consent and conduct of research will be met.

c. The proposed research is considered essential.

d. No adverse publicity or political impact can be foreseen.

e. No. DOD or Army regulations or policies will be violated.

f. Subjects are available and no specific requests for additional subjects need be made.

g. There will be negligible interruption of training or missions imposed by the research.

h. Discomfort and risk to subjects will be minimal.

2. While the procedure outlined above has not come under question, it has not been formally approved by the Director of Army Research. Approval, denial or modification of the procedure is requested.

/s/

DONALD L. HOWIE
Colonel, GS
Chief, Life Sciences Division

Annex G

#

CRD/H (20 Apr 64)
SUBJECT: AR 70-25

TO: The Surgeon General FROM: CRD DATE 25 MAY 1964 COMMENT NO. 2

1. The information contained in Comment #1 has been carefully evaluated in order to determine the benefits to be derived from incorporating the recommended changes in subject AR.

2. The wording and content of AR 70-25 was developed only after a complete DA staffing and includes, in addition to the specific requirements for the medical aspects involved, those of a legal and moral nature for maximum protection of all concerned.

3. The following comments pertain to the respective subparagraphs of paragraph 2, Comment #1.

a. Subparagraph a. The addition of the statement, "The Surgeon General's recommendation concerning medical aspects of research using human subjects shall be binding on all commands and agencies" is considered to be unnecessary. The Surgeon General is recognized by the General Staff, and particularly by this office, to be the principal advisor to the Chief of Staff on medical matters. It is, furthermore, the Chief of Research and Development's policy that, in matters pertaining to medical aspects of research, your recommendations will be respected. Final approval of all requests to use human subjects in research is given contingent upon compliance with your recommendations on the medical aspects of the experiment.

b. Subparagraph b. It is the policy of this office to seek the approval of the Secretary of the Army for all research wherein human volunteer subjects are exposed to ionizing radiation from any type of source. It should, however, be emphasized that the use of radioactive isotopes in medical diagnosis and therapy for patients is not within the purview of AR 70-25, nor are experimental clinical procedures undertaken on a patient for his benefit, as provided by par 3c, AR 70-25.

c. Subparagraph c. The word "ethical" was recommended during the staffing of the Army Regulation to emphasize that all U. S. Army medical practices are considered to be in strict accordance with the highest standards of ethics. However, to avoid any misinterpretation, the word "ethical" will be deleted at such time as the Army Regulation requires substantive revision.

d. Subparagraph d. The wording as contained in paragraph 5d, is based on your recommendations contained in Comment #2, MEDDH, dated 23 June 1961, subject: Draft Army Regulation in Use of Human Volunteers in Research Programs to Obtain Psychological and/or Biological Data. It is considered more appropriate to arrange for consultant service on short notice for any anticipated difficulties which may be encountered during the experiment with volunteers.

Comment #1

CRD/N (20 Apr 64)
SUBJECT: AR 70-25

4. Insuring the proper utilization of volunteers in research is considered of such importance that all possible precautionary measures must be rigidly followed to provide the maximum protection to the volunteers, investigators and the Government. It is essential that all personnel having responsibilities in programs in which human beings are used as subjects of research adopt a positive, constructive attitude of compliance with the provisions of AR 70-25 to insure that this vital aspect of Army biomedical research is not restricted or prohibited.

SIGNED

G. W. POWER
Major General, GS
Acting Chief of Research
and Development

CRD/N

1 December 1965

MEMORANDUM FOR RECORD

SUBJECT: Approval for Requests for Use of Human Volunteers in Research

1. References:

a. AR 70-25

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5. A copy of this memorandum should be permanently maintained in the "Human Volunteers" files.

THOMAS R. OSTROM
Lt Colonel, GS
Life Sciences Division

CRDLS 11 June 1968

MEMORANDUM FOR: DIRECTOR OF ARMY RESEARCH

SUBJECT: AR 70-25 "Use of Volunteers as Subjects of Research"

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a. No. NBC agents are involved.

b. All provisions of AR 70-25 concerning consent and conduct of research will be met.

c. The proposed research is considered essential.

d. No adverse publicity or political impact can be foreseen.

e. No. DOD or Army regulations or policies will be violated.

f. Subjects are available and no specific requests for additional subjects need be made.

g. There will be negligible interruption of training or missions imposed by the research.

h. Discomfort and risk to subjects will be minimal.

2. While the procedure outlined above has not come under question, it has not been formally approved by the Director of Army Research. Approval, denial or modification of the procedure is requested.

/s/

DONALD L. HOWIE
Colonel, GS
Chief, Life Sciences Division

CRD/H (20 Apr 64)
SUBJECT: AR 70-25

TO: The Surgeon General FROM: CRD DATE 25 MAY 1964 COMMENT NO. 2

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2. The wording and content of AR 70-25 was developed only after a complete DA staffing and includes, in addition to the specific requirements for the medical aspects involved, those of a legal and moral nature for maximum protection of all concerned.

3. The following comments pertain to the respective subparagraphs of paragraph 2, Comment #1.

a. Subparagraph a. The addition of the statement, "The Surgeon General's recommendation concerning medical aspects of research using human subjects shall be binding on all commands and agencies" is considered to be unnecessary. The Surgeon General is recognized by the General Staff, and particularly by this office, to be the principal advisor to the Chief of Staff on medical matters. It is, furthermore, the Chief of Research and Development's policy that, in matters pertaining to medical aspects of research, your recommendations will be respected. Final approval of all requests to use human subjects in research is given contingent upon compliance with your recommendations on the medical aspects of the experiment.

b. Subparagraph b. It is the policy of this office to seek the approval of the Secretary of the Army for all research wherein human volunteer subjects are exposed to ionizing radiation from any type of source. It should, however, be emphasized that the use of radioactive isotopes in medical diagnosis and therapy for patients is not within the purview of AR 70-25, nor are experimental clinical procedures undertaken on a patient for his benefit, as provided by par 3c, AR 70-25.

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Comment #1

CRD/N (20 Apr 64)
SUBJECT: AR 70-25

4. Insuring the proper utilization of volunteers in research i considered of such importance that all possible precautionary measu must be rigidly followed to provide the maximum protection to the volunteers, investigators and the Government. It is essential that personnel having responsibilities in programs in which human beings used as subjects of research adopt a positive, constructive attitud compliance with the provisions of AR 70-25 to insure that this vita aspect of Army biomedical research is not restricted or prohibited.

SIGNED

G. W. POWER
Major General, GS
Acting Chief of Research
and Development

NASA - Ames

Moffett Field, California
January 20, 1969

Not transmitted to Hdqts.

MEMORANDUM for Director

From: Mr. George A. Rathert, Jr., Chairman, Human Research Experiments Review Board, Code FL

Subject: Proposed Investigation entitled "Measurement of Cerebral Blood Flow in Man by an Isotopic Technique Employing External Counting", by Dr. Leo A. Sapierstein, Stanford University

Reference: Memo to G. Rathert from L. Bright, January 7, 1969, subject as above, LGB:kh, w/enclosure

1. The Human Research Experiments Review Board met on January 15, 1969 to consider the subject proposal. All members were present.

2. The Board recommends that the subject proposal be approved subject to the following understanding and comments:

a. It is the Board's understanding that as stipulated in the comments on the Ames Proposal Evaluation Report (Item 10, Form 884, attached), patients who would in any case be given the isotope are to be used as subjects instead of the "normal" subjects suggested for Phase II in the proposal. This change should be stipulated in the signed agreement.

b. The Special Consent Form, Appendix III of the Proposal, is considered by the Board to be deficient with respect to notifying the patient that he is consenting to be a subject in experimental research. A suggested revision is attached.

c. The maximum permissible dose of the isotope and maximum amount of local radiation should be stipulated in writing.

d. The compositions of ambient air and method and duration of exposure of the subject (face mask) proposed for Phase 5 should be stipulated, particularly since NASA Headquarters occasionally prohibits Centers from authorizing or sponsoring experiments of specific types (e.g., 100% oxygen in a closed chamber). Any inconveniences or risks to the patient resulting from breathing these altered gas mixtures should be included in the Special Consent Form.

e. On page 5 of the proposal, it is considered that the wording should indicate the proposal must be approved by the Stanford Committee for Institutional Assurance.

3. The Board recommends to the Director that the Technical Monitor be notified by his Division Chief, in writing, of his responsibility to monitor compliance with the provisions of AMM 7170-I.

1-21-69

George A. Rathert, Jr.
Chairman, Human Research Experiments
Review Board

HJA
JFP

GAR GAR:dcl 1-20-69

Encls.
Ref. Memo w/enclosure
Revised Appendix III

cc: Ea Board Member w/o encs
R. G. Robinson w/o encs.

Ames Research Center
Suggested Revision

APPENDIX III

SPECIAL CONSENT FORM

PART I

1. During the course of diagnostic evaluation for your illness, a radioactive isotope, Technetium ^{99m} will be used. It is likely that the information obtained with this isotope will be of help to your doctor in deciding whether or not further treatment is necessary. We would further like to use data obtained through the use of the isotope for a research study.

2. Title. Measurement of Cerebral Blood Flow in Man by an Isotopic Technique Employing External Counting.

3. Principal Investigators.

Leo A. Sapierstein, M.D.
Wm. Marshall, M.D.

4. Nature of Studies. Technetium ^{99m} will be injected into an arm vein. Counters will be placed over your heart and head, and occasionally arterial blood will be withdrawn. The counts obtained will make it possible to measure the flow of blood through both heart and head. We believe that the information obtained regarding your circulation will allow us to make a better decision about your treatment, and will aid others suffering from similar ailments.

5. Foreseeable Inconvenience, Risks, and Discomfort.

a. Phases 2, 3, and 4 - The part of the procedure you are consenting to which principally benefits the research program and is not part of your treatment is known as an arterial puncture. This procedure has been used at the Stanford University Hospital for a considerable number of years and the risks involved are minimal in the hands of the experienced personnel who will be involved. These risks will be explained to you in detail if you so desire. The entire procedure, including the diagnostic radioscan, takes about an hour.

b. Phase 5 - (Include here the composition of the gas mixtures to which the patient will be exposed, and any foreseeable inconvenience, risk, or discomfort he may experience.)

DEPARTMENT OF THE NAVY
OFFICE OF THE SECRETARY
WASHINGTON, D. C. 20350

RCC1.950125.001c

SECNAVINST 3900.39
OP [illegible]
Ser [illegible]2
28 April 1969

SECNAV INSTRUCTION 3900.39

From: Secretary of the Navy
To: Distribution List

Subj: Use of volunteers as subjects in research, development, test, and evaluation

Ref: (a) Manual of the Medical Department Chapter 2[illegible], Research and Development, Paragraph 20-8, Use of Volunteers in Hazardous Experiments

Encl: (1) Sample Human-Volunteer Consent Document

1. Purpose. To prescribe policies and procedures of the Department of the Navy governing the use of volunteer subjects in research, development, test, and evaluation (RDT&E) conducted by, within, or for the Naval Establishment wherein human beings are experimentally exposed to hazardous conditions or materials. This Instruction does not apply to the use, in the treatment of individual patients, of drugs approved by the Federal Drug Administration for investigational use only. It does apply to the use of investigational drugs under an approved RDT&E project or task in a volunteer population of healthy persons or a volunteer population of patients in which the experimental drug testing has no relationship to the cause of their being on the sick list.

2. Background. In the use of volunteers as subjects in hazardous experimental situations, it is obvious that military R&D commanders, scientific and technical program managers, and project directors have special responsibilities both moral and legal in nature. It has long been recognized that hazardous experiments utilizing human test subjects are absolutely necessary to extend the frontiers of medical science, aerospace flight, and undersea exploration. The atrocities which were committed against human beings during the Second World War served as a decisive factor in the adoption by the World Medical Association of a clearly stated code of medical ethics. It is accepted United States national and Department of Defense policy that the use of human subjects be based upon voluntary, informed consent and be confined to experiments or tests which are necessary, scientifically sound, and reasonably safe.

3. Definitions. For the purpose of this Instruction, hazardous conditions or materials are those which present risk of privation, discomfort,

distress, pain, physical or mental injury, or death greater than the hazards inherent in training or work within accepted occupational parameters.

4. Policy. Certain basic principles must be observed to satisfy moral and legal concepts. These are:

a. Voluntary consent is essential.

(1) The volunteer must have legal capacity to give consent. He will be so situated as to be able to exercise free power of choice, without the intervention of any element of force, deceit, duress, or ulterior form of constraint or coercion. He will have sufficient knowledge and comprehension of the elements of the subject matter involved to enable him to make an understanding and enlightened decision. Such knowledge will be provided to the volunteer in such a manner as not to compromise the experiment. Thus he will be told, prior to acceptance of his consent, the nature, approximate duration, and purpose of the experiment; the method and means by which it is to be conducted; and the inconveniences and hazards entailed -- all in such a way as not to invalidate the results. He will be fully informed of the effects upon his health or person which may possibly result from his participation in the experiment. He will be made to understand clearly that, at any time during the course of the experiment, he will have the right to revoke his consent and to withdraw from the experiment without prejudice to himself.

(2) The document of consent will be in writing, setting forth the above requirements and containing, or having attached and referenced, a summary of the information given to the volunteer pursuant to the foregoing requirements. It shall also contain a statement by the volunteer that he is not relying upon any information or representation not set forth in the document of consent and that his consent is given as an exercise of free will, without any force or duress of any kind. The document will be signed by the volunteer -- over his full name; his rank, rate, grade, or title; and his date of birth -- in the presence of at least one witness who is not directly involved in the experiment or test and who will attest to such signature in writing. Enclosure (1) provides a sample of an acceptable volunteer consent document, the original of which will remain in the records of the activity conducting the test.

(3) The responsibility for ascertaining the validity of the consent rests upon the person who directs the experiment or test. It is a personal responsibility which may not be delegated.

b. The number of volunteers used will be kept at a minimum consistent with sample-size requirements necessary for scientifically valid conclusions.

c. The experiment must be such as to contribute to an approved naval RDT&E project. In addition, the experiment or test should be such as to yield fruitful results for the good of society, unobtainable by other methods or means of study, and not random and unnecessary in nature. There will be reasonable anticipation that the results will justify the performance of the experiment or test. Accordingly, all experiments and tests will be based upon prior study or experimentation and designed to accomplish this objective. All medical experiments or experiments involving the use of an experimental drug should be based upon the results of animal experimentation and a knowledge of the natural history of the disease or other problem under study.

d. The experiment or test will be conducted so as to avoid unnecessary physical or mental stress. No experiment or test will be conducted if, upon careful consideration by the person who directs the experiment, there is reason to believe that death or disabling injury will occur. The degree of risk to be taken will never exceed that determined to be justifiable by the humanitarian importance of the problem to be solved by the experiment. Proper preparations will be made under the supervision of a qualified physician, knowledgeable in the test field, and with adequate medical facilities and safety equipment being provided to protect the volunteer against the possibilities of injury, disability, or death. Adequate and complete medical treatment will be available for treatment of casualties. The physician-in-charge will have consultants, available on short notice, who are competent to advise or assist with unexpected complications.

e. The experiment or test will be directed only by scientifically qualified persons with a high degree of technical and professional competence in conducting such procedures. All personnel supervising or participating in such procedures must be adequately trained to perform their duties reliably in foreseeable circumstances. The highest degree of care will be required at all stages of the experiment or test.

f. Volunteers will have no physical or mental diseases which will make the proposed experiment more hazardous for them than for normal healthy persons. This determination will be made by the experiment or test director on the basis of competent medical advice.

g. The experiment or test director, or his acting subordinate, will exercise careful judgment, superior skill, and good faith at all

times during the course of the experiment or test. The director will terminate the procedure at any stage if it is likely that continuation will result in injury, disability, or death to a volunteer. During the course of an experiment or test, a volunteer shall be at liberty to revoke or withhold his consent and to withdraw, without prejudice to himself, from the experiment or test, or from a portion thereof. New dangers and adverse developments arising during the course of the experiment or test, about which the volunteer has not been briefed or warned, shall be reported to the volunteer in a timely manner unless such communication would pose an immediate threat to his safety.

c. Prisoners of war will not be used under any circumstances.

5. Procedures

a. The experiment or test director will prepare a written request for approval of the use of volunteers in any proposed procedure coming within the purview of this Instruction. The request will include the names of the director and the conducting activity and the identity of the responsible supporting medical activity. It will speak appropriately to the principles of policy guidance expressed in paragraph 4 of this Instruction. The request will enclose a plan of the experiment or test consistent with security requirements.

b. The request will be forwarded via (1) the appropriate military chain of command; (2) the Chief, Bureau of Medicine and Surgery; (3) the Chief of Naval Personnel/Commandant of the Marine Corps, or both, as appropriate; and (4) the Chief of Naval Operations (OP-07(DEV)) to the Secretary of the Navy (ASN(R&D)).

(1) The RDT&E chain of command endorsements are to be directed primarily to the technical soundness and program importance of the experiment or test for which the use of human volunteers is proposed.

(2) The Chief, Bureau of Medicine and Surgery, will direct his endorsement specifically to the degree of hazard inherent in the test, the adequacy of safety measures, the adequacy of medical supervision and support, and the adequacy of the human-volunteer consent statement to be utilized.

(3) The Chief of Naval Personnel/Commandant of the Marine Corps will direct their respective endorsements in particular to the utilization of active-duty military personnel in existing billets for voluntary duty as experimental subjects, and to other aspects as they deem appropriate.

(4) The Chief of Naval Operations (OPNAV(OPEV)) will direct his endorsement to the validity of the requirement for doing the experiment; the adequacy of the certification by BUMED on pertinent medical aspects; the approved utilization of personnel in the manner proposed; and the statement of program need by the sponsoring command. Administrative and coordination action will be assigned to the Staff Assistant for Medical and Allied Sciences.

(5) The Assistant Secretary of the Navy (Research and Development) will act as approving authority for the Secretary of the Navy. Review of legal aspects will be accomplished by the Office of the Judge Advocate General.

6. Management. Since the use of volunteers in experimental or test situations is an integral part of the conduct of the RDT&E Program and does not involve the establishment of additional manpower billets, action on such requests, including coordination of manpower and legal aspects, will be through the RDT&E chain of command.

7. Implementation. Addressees are authorized to take such action as is necessary to assure compliance with this Instruction throughout the Naval Establishment.

JOHN W. WARNER
Under Secretary of the Navy

Distribution (See page 6)

SAMPLE FORM

SECNAVINST 3900.39
28 April 1969

NAME OF ACTIVITY

CONSENT TO PARTICIPATE VOLUNTARILY IN A RESEARCH, DEVELOPMENT, TEST, & EVALUATION (RDT&E) PROCEDURE

DATE _____

1. I hereby volunteer to participate as a subject in an RDT&E procedure being conducted under Element No. _____, Project No. _____; Work Unit Title "_____", which has been approved by _____. I understand
(sponsoring command)
that the adequacy of safety measures has been certified by the Chief, Bureau of Medicine and Surgery, and that authority to use human volunteers has been granted by the Secretary of the Navy.

2. The nature and purpose of the procedures have been explained to me as follows: (See attached summary.)

3. In making my decision to volunteer, I am not relying upon any information or representation not set forth in this document, or attached summary. My consent is given as an exercise of free will, without any force or duress of any kind. I understand that my consent to participate does not constitute a release from any possible future liability by the United States attributable to the experiments.

SIGNED: _____

_____
(TYPED NAME, RANK, RATE, OR GRADE)

DATE OF BIRTH _____

WITNESSED: _____
(NOT DIRECTLY INVOLVED IN TEST)

APPROVED: _____

_____
(TEST DIRECTOR)

Copy to:
Service record, jacket, or personnel file

Enclosure (1)

NMD/AD 7100.9

February 2, 1972

Effective date

Management Delegation

SUBJECT: POWER AND AUTHORITY--TO AUTHORIZE HUMAN RESEARCH AND TO GRANT CERTAIN RELATED EXCEPTIONS AND WAIVERS

1. DELEGATION

The Director of each NASA Field Installation and, for NASA Headquarters, the NASA Director of Life Sciences, is empowered, subject to conditions and limitations imposed by immediate superiors, to authorize human research, as defined in and within the scope of NMI 7100.8 , and to grant exceptions and waivers in connection with human research, subject to the provisions of NMI 7100.8 ; provided that when he is or anticipates acting as an investigator with respect to a particular proposed human research, he shall request authorization therefor from the Administrator.

2. REDELEGATION

All or part of the authority may be redelegated, without power of further redelegation, to one of the following positions (such redelegation shall be published in the installation issuance system):

a. To a NASA employee who reports directly to him, or

b. To the installation medical officer if an employee of NASA.

3. REPORTING

The officials to whom authority is delegated in this NMD shall ensure that feedback is provided to the Administrator through official channels to keep him fully and currently informed of significant actions, problems, or other matters

of substance related to the exercise of the authority delegated hereunder.

George M. Low

Deputy Administrator

DISTRIBUTION

SDL 1

NMI 7100.4

February 2, 1972
Effective date

Management Instruction

SUBJECT: HUMAN RESEARCH POLICY AND PROCEDURES

1. PURPOSE

This Instruction sets forth NASA policies and procedures relating to the conduct of human research.

2. SCOPE AND APPLICABILITY

a. This Instruction is applicable to NASA Headquarters and Field Installations.

b. This Instruction applies to all human research conducted by NASA, by or under the direct supervision of a NASA officer or employee or an officer or employee detailed to NASA from another Government agency.

c. This Instruction does not apply to human research conducted by NASA contractors or NASA grantees under a contract or grant. Nor does it apply to human research conducted under a cooperative arrangement or agreement entered into by NASA and another Government agency, private entity, or non-Federal public entity. The provisions of the contract, grant, cooperative arrangement or agreement shall govern the conduct of such human research.

3. Authority

Section 203(b)(1) of the National Aeronautics and Space Act of 1958, 42 U.S.C. 2473(b)(1).

4. DEFINITIONS

For the purposes of this Instruction, the following definitions apply:

a. The term "human research" means any test, experiment or other evaluative procedures involving a human subject.

b. The term "human subject" means any person who is an integral part of a test, experiment or other evaluative procedure. For example, a person would be a human subject if the test, experiment or other procedure is conducted to evaluate, or to change and evaluate, any condition, response or performance of (1) that person; or (2) the equipment, article or other substance inserted in, applied to, operated or otherwise used by, on or in that person.

c. The term "principal investigator" means any NASA official who is directly in charge of the human research.

d. The term "authorized NASA official" means the NASA employee who has been delegated or has been redelegated authority to conduct human research pursuant to NMD/AD 7100.9.

5. REQUIREMENTS, EXCEPTIONS, AND WAIVERS

a. Except as provided in this paragraph 5, all human research within the scope of this Instruction shall be conducted in accordance with the requirements set forth in paragraphs 6 through 11. Notwithstanding this paragraph 5, in no event shall there be an exception to or waiver of the proscription in paragraph 7.

b. Unless an authorized NASA official provides otherwise in light of special circumstances, the provisions of this Instruction shall not apply to a test, experiment or other evaluative procedure:

(1) Required or authorized by the Civil Service Commission or by other Government agency's regulations to be performed on, or with respect to Government employees or applicants for Government employment for the purpose of determining their qualifications

or suitability for employment or for the purpose of ascertaining or maintaining employees' health.

(2) As determined by the principal investigator, that is (a) performed by or under the supervision of a physician (who may be the principal investigator) for the purpose of diagnosing, preventing, curing or alleviating disease in a particular human subject (b) performed primarily for the human subject's benefit; and (c) recognized generally by the medical profession as proper.

(3) Involving as a human subject a specially trained adult who knowingly follows a specialized calling or occupation generally recognized as hazardous, and for whom the test, experiment or evaluative procedure forms an integral part of his calling or occupational performance. For example, a test, experiment or evaluative procedure concerning air or space flight and involving a test pilot or astronaut as the human subject ordinarily would fall within this exception. However, if a test pilot or astronaut is asked to serve as a human subject in an experiment requiring, for example, cardiac catheterization, the human research would not fall within this exception; this human research could not reasonably be considered as within the scope of his specialized calling or occupation.

(4) Involving as a human subject a NASA career or career conditional employee, or a NASA employee in an excepted position with indefinite tenure, whose regular position description (which describes his duties and responsibilities) requires or may be reasonably construed as contemplating the employee's participation in the test, experiment or other evaluative procedure

c. Unless an authorized NASA official provides otherwise in light of special circumstances, the following human research, as determined by the principal investigator, shall be subject only to the requirements set forth in paragraphs 6, 7, 9a and 9b: Those tests, experiments or other evaluative procedures that would not expose a human subject to a risk of distress, pain, impairment of health,

physical injury, personality or emotional disorder or death. This determination shall be made by the principal investigator in light of his knowledge and experience; it shall be made in such form and be subject to such review, if any, as the authorized NASA official may provide.

d. The requirements set forth in paragraph 6 and 8 may not be necessary in exceptional cases, for various reasons, to protect the subjects of certain human research. When the principal investigator of proposed human research believes this to be the case, he may submit to the cognizant authorized NASA official a request that some or all of the requirements of paragraphs 6 and 8 be waived and the following procedures apply:

(1) The request shall be submitted with a description of the proposed human research prepared in accordance with Attachment A or, when appropriate, in some other less comprehensive form.

(2) Upon receipt of the request, the authorized NASA official may, in his discretion, grant or deny the waiver request in full or in part, or require the submission of further information concerning the proposed human research.

(3) When a waiver has been obtained pursuant to the provisions of this subparagraph d, the human research shall not be changed unless such change is approved by the authorized NASA official, and a new waiver, as appropriate, obtained. The informed consent of the human subject should be obtained to the research as changed unless in an exceptional case that requirement has been waived.

6. VOLUNTARY INFORMED CONSENT

a. No human research may be conducted unless the human subject voluntarily gives his informed consent in writing to participate in the proposed human research and has the legal capacity to so consent.

b. No consent given by a human subject shall be deemed in-

formed unless, prior to the giving of consent, the proposed human research is explained to the human subject in language understandable to him. Such explanation must include the nature, duration, and purpose of the human research; the manner in which it will be conducted; and all reasonably foreseeable risks of injury, death, inconvenience or discomfort to the subject from the human research. The human subject must be informed that the extent or nature of such risks is not known, if that is the case. In addition, the human subject must be informed that he may withdraw from the human research at any time or, if this is not in fact the case (because unwise, dangerous, or impossible), he must be so advised.

c. Written consent shall be obtained in such form as will indicate that the human subject has been fully informed of, and voluntarily accepts, the risks, inconveniences and discomforts which may be involved.

7. RIGHTS OF SUBJECTS

No human subject shall be asked to waive any rights that may arise against the United States in connection with any injury, loss, illness, disease or death suffered by the subject as a result of human research.

8. PROTOCOLS AND AUTHORIZATION OF HUMAN RESEARCH

a. No human research may be conducted unless:

(1) The principal investigator has submitted to the authorized NASA official a protocol prepared in accordance with Attachment A; and

(2) The authorized NASA official, after obtaining the advice described in paragraph 11 and after considering the protocol of the principal investigator, authorizes in writing human research in accordance with the protocol as submitted, or in accordance with the protocol revised in such manner as the authorized NASA official may determine.

b. In determining whether the proposed human research should be authorized, the authorized NASA official will consider

AUG

among other things, whether:

(1) The importance of the objective of the research outweighs the inherent risks to the subject.

(2) The subject of the human research will be unnecessarily exposed to risk of injury, illness, disease, death, discomfort or inconvenience.

(3) The subject or his representatives will be compensated, by reason of insurance, workmen's compensation, or the like, in the event the subject suffers loss, injury, illness, disease or death as a result of the human research.

c. Human research, once authorized under subparagraph a., shall not be changed if such change affects any item of the protocol unless such change is approved by the authorized NASA official and the informed consent of the human subject is obtained.

9. REPORTS OF INJURIES, ILLNESS OR DISEASE AND CHANGES IN PROCEDURES

The principal investigator of human research shall immediately suspend the human research (unless such suspension would endanger the human subject) and inform the authorized NASA official in the event of:

a. Any injury, illness or disease to the subject.

b. Any change in the environment or the subject's response that could lead to some medical disturbance.

c. Any change from (1) the human research as described in the approved waiver request submitted pursuant to paragraph 5 or (2) the approved protocol submitted pursuant to paragraph 8.

*10. COMMITTEES

Pursuant to NMD/A 1150.7 and NMI 1150.1, each Field Installation Director, in his discretion, may appoint a committee composed of installation employees to advise the authorized

*Changed by this Revision

NASA official on matters within the scope of this Instruction. Similarly, for NASA Headquarters, the Associate Administrator for Center Operations may appoint a committee composed of NASA employees for the same purpose. If the establishment of an advisory committee, which will include non-Government members, is believed to be desirable, then the provisions of NMI 1150.2 shall be followed.

11. LEGAL, SAFETY AND MEDICAL OFFICE REVIEWS

a. A copy of the waiver request submitted pursuant to paragraph 5d, or the protocol submitted to the authorized NASA official in accordance with paragraph 8, shall be submitted to the appropriate installation counsel's office, the installation safety office and the installation medical officer for their advice within a reasonable time before the conduct of human research.

b. The authorized NASA official shall obtain the advice of the installation counsel's office, the installation safety office and the installation medical officer prior to acting pursuant to paragraph 5d or 8.

12. IMPLEMENTING INSTRUCTIONS BY FIELD INSTALLATION

A copy of any installation implementing instruction shall be forwarded to the General Counsel, NASA Headquarters.

James C. Fletcher
Administrator

ATTACHMENT:
A. Content of Protocol

DISTRIBUTION:
SDL 1

CONTENT OF PROTOCOL

The protocol to be submitted to an authorized NASA official in accordance with paragraph 8 shall provide the following information:

1. The title of the proposed research.

2. Name of NASA organization conducting the research or for which the research is being conducted.

3. Name and qualification of principal investigator (and of co-investigators, if any).

4. Name and qualifications of persons who will conduct the human research (unless covered in item 3).

5. The purpose of the research, including an explanation of why the use of human subject is required.

6. The plan of study.

7. Historical background of the research, with references to pertinent scientific literature. This should include a discussion of relevant prior research using human beings and/or animals.

8. A hazards analysis, a description of the hazards controls and safety precaution to be applied, and an assessment of residual risks. Will an Operational Readiness Inspection be conducted prior to the conduct of the human research?

9. Expected duration of the study. (Give approximate beginning and ending dates.)

10. Approximate number of subjects to be used.

11. The source(s) from which subjects are to be obtained.

12. Criteria to be used in selecting subjects.

13. Possible inconveniences, discomforts, illness, disease, pain, and risks to the subjects.

14. The extent of the physical examination to be given by a physician: (1) initially to ascertain that the subject's health status has been adequately established to certify that he is capable of undertaking the research/test, (2) during the course of the research, and (3) at the completion of the research.

15. Will the subject be free to withdraw from the research at any time? If not, explain why; when and under what circumstances may the subject withdraw?

16. Wage, salary, or other payment, if any, to be paid to the subject.

17. Will the human subject's identity be disclosed, or be made available on request, to the public? The identity of the human subject will not be made available to the public without his consent.

18. Source (Federal or state compensation acts, insurance, other) and general description (include example of dollar amounts) of compensation, if any, to be received by a subject or his representative in the event of injury or death. Assistance in the preparation of this information may be obtained from the appropriate installation counsel's office or, if the subject is, or will be, a Government employee, the installation personnel office.

19. Availability of a physician and an adequate medical facility within a reasonable distance during the research. (Indicate whether a physician will be present at all times or on call; if on call, his location during the performance of the research.)

20. What information concerning the human research is intended to be communicated to the subject in the course of obtaining his consent? (See paragraph 6 of the Instruction.)

21. The proposed form of consent the subject will be asked to execute.

22. If a determination pursuant to paragraph 5d has been, or will be, requested, the [illegible] should so indicate.

S15 15 Oct 1981

*AR 40-38

ARMY REGULATION
No. 40-38

HEADQUARTERS
DEPARTMENT OF THE ARMY
WASHINGTON, DC. 28 February 1973

MEDICAL SERVICES
CLINICAL INVESTIGATION PROGRAM

Effective 1 April 1973

This revision reflects continually changing legal requirements in the field of human investigation. Local supplementation of this regulation is prohibited except upon approval of The Surgeon General (DASG).

1. Purpose. This regulation provides Army policy guidance for clinical investigations funded under other than the RDTE appropriation and prescribes the procedures for processing proposals and for reporting progress.

2. Applicability. *a.* The provisions of this regulation are applicable to all Army medical facilities and activities.

b. The provisions of this regulation are not applicable to proposals regarding health care research as defined below.

3. Definitions. *a. Clinical investigation.* Under this program clinical investigation consists of the organized scientific inquiry, both in humans and by directly related laboratory work, into clinical problems of significant concern in the necessary health care of members of the military community, including active duty personnel, dependents, and retirees.

b. Health care research. The application of scientific methods to the study of the availability, organization, administration, and management of health services to include the efficiency and effectiveness with which such services are delivered.

c. Subjects. Any persons who may be at risk because of participation as an object of clinical investigation by members of the AMEDD or their appointed representatives. These may include inpatients, outpatients, organ donors, informants, or normal individuals who participate in studies of medical, physiological, sociological, or psychological orientation.

d. At risk. A person is "at risk" if he/she may be exposed to the possibility of harm (physical, psychological, or sociological) as a consequence of activity which extends beyond use of established and accepted methods necessary to meet his/her needs. Determination of nature and extent of "at risk" is a matter of commonsense and professional judgment. Responsibility for this determination resides at all levels of institutional and departmental review. Definitive determination will be made by the operating agency.

4. Policy. *a.* It is the policy to encourage the performance of clinical investigation by AMEDD personnel, especially by personnel assigned to Army hospitals where post-graduate educational programs are conducted.

b. Within these Army teaching hospitals, basic personnel support for clinical investigation is a matter of hospital staff authorization.

(1) Since resources are limited and the procedures unique, clinical investigation support personnel should be organized within a separate Clinical Investigation Service of the hospital organization structure. The Chief of the Clinical

*This regulation supersedes AR 40-38, 30 August 1971.

TAGO 405A—February 510-472—73

Investigation Service will serve as coordinator of clinical investigation for the hospital commander.

(2) The commander of the hospital will appoint the following committees from the professional staff:

(*a*) *Clinical Investigation Committee*—To review all clinical investigation proposals for scientific adequacy and to set priorities for support. This committee will be composed of the Chief, Professional Service or his designated representative who will act as Chairman, and at least six other medically qualified individuals designated by the hospital commander.

(*b*) *Human Use Committee*—To review for medical safety and suitability all clinical investigation protocols involving the use of human subjects. This committee will be composed of the Chief, Professional Services, who will act as Chairman, a Chaplain, a JAG officer and four other qualified individuals designated by the Commander of the hospital, who are not members of the Clinical Investigation Committee.

(3) The Chief, Clinical Investigation Service will serve as the recorder of the Clinical Investigation and Human Use Committees. He will be responsible for maintaining records of all actions pertaining to individual protocols.

(4) Where appropriate in Army non-teaching hospitals, the Chief, Professional Service may serve as coordinator of clinical investigation activities.

c. The moral, ethical and legal concepts relating to the use of human subjects will be followed as outlined in AR 70–25. The voluntary consent of the human subject is essential. Each individual who initiates or directs the clinical investigation has a personal duty and responsibility for ascertaining the quality of the subject's consent. Before the acceptance of the subject, he must be given adequate explanation. He should be informed of the nature, duration, and purpose of the study; the method and means by which it is to be conducted; all inconveniences and hazards reasonably to be expected; and the effects upon his health or person which may possibly come from his participation in the study. The agreement will be prepared in accordance with the format outlined in appendix A, and will be in non-medical language that is easily understood by the subject.

d. Resource requirements for the Clinical Investigation Program will be programed and budgeted through established program/budget procedures.

e. Clinical investigation projects should be oriented toward clinical problems of significant concern in the necessary health care of the military community.

f. Investigation objectives should allow conclusion of studies within the anticipated tour of the investigator, or careful plans should be made to permit continuation when the investigator leaves.

g. Proposals in the following categories must be approved by The Surgeon General prior to initiation of investigation:

(1) When funding requirements exceeds $5,000.

(2) When human subjects are used.

(3) When investigational drugs are employed in humans, or any use is made of Schedule I controlled substances. See AR 40–7.

(4) When radioisotopes are used. See AR 40–37.

(5) When a proposal is submitted from an Army hospital not having a clinical investigation service.

(6) When the proposal is concerned with drug or alcohol abuse.

5. **Submission of proposals.** *a.* Proposals will be prepared in accordance with the format outlined in appendix B. All appropriate paragraphs will be completed and the information on the background data, problem, experimental design, and method of approach will be sufficient to facilitate evaluation.

b. Completed proposals will be submitted to the local commander or his designated representative (para 4*b*) for critical review. The proposal will be evaluated for scientific validity, need, practicality, personnel, and funding requirements. Unsatisfactory or incomplete proposals will be returned to the originator without further action.

c. Satisfactory proposals will be submitted to the local Clinical Investigation and Human Use Committees for approval. Approved proposals will then be submitted to the commander for approval.

d. Proposals not subject to prior approval as outlined in paragraph 4*g* will be forwarded through channels to The Surgeon General, HQDA

(DASG) WASH DC 20314 for information only.

e. Proposals falling within the requirements of paragraphs 4*g*(1), (2), (4), 5) or (6) will be forwarded through appropriate channels to The Surgeon General, HQDA (DASG) for evaluation and approval.

f. Proposals falling within the requirements of paragraph 4*g*(3), will be processed as provided in *a*, *b* and *c*, above, and in addition will have an application prepared as prescribed in paragraph 3*b* or *c*, AR 40-7. Such proposals will be forwarded as prescribed in AR 40-7.

g. Forwarding correspondence should include all action taken on the proposal by the local Clinical Investigation and Human Use Committees (para 4*b*).

6. Reporting requirements. Activities and/or individuals undertaking clinical investigation will submit an annual progress report entitled, Clinical Investigation Program Reports Control Symbol MED-300, following the guidelines set forth in appendix C. Prior to final printing and distribution, two draft copies will be submitted to The Surgeon General, HQDA (DASG) WASH DC 20314 for format review within 30 working days after the close of the fiscal year.

7. TSG clinical investigation and human use committees. A DASG Clinical Investigation Committee and a Human Use Committee will be established to review all proposals for approval submitted to The Surgeon General as specified in paragraph 4*g*.

APPENDIX A

VOLUNTEER AGREEMENT

I, _____ having attained my eighteenth (18th) birthday, and otherwise having full capacity to consent, do hereby volunteer to participate in an investigation study entitled:

_____

_____

under the direction of _____.

The implications of my voluntary participation; the nature, duration and purpose; the methods and means by which it is to be conducted; and the inconveniences and hazards to be expected have been thoroughly explained to me by _____, and are set forth in full on the reverse side of this Agreement, which I have initialed. I have been given an opportunity to ask questions concerning this investigation study, and any such questions have been answered to my full and complete satisfaction.

I understand that I may at any time during the course of this investigation study revoke my consent, and withdraw from the study without prejudice; however, I may be required to undergo certain further examinations, if, in the opinion of the attending physician, such examinations are necessary for my health or well being.

_____ _____
Signature Date

I was present during the explanation referred to above, as well as the Volunteer's opportunity for questions, and hereby witness his signature.

_____ _____
Witness' Signature Date

On this side of the Volunteer Agreement, the principal investigator should set forth full details concerning the investigation study, insofar as such would affect or influence the tentative subject in any way. This explanation should be worded so that it can be clearly understood by the subject. The subject should place his initials at the end of the last line of explanation.

A proper explanation should, at a minimum, provide the answers to the following questions:

1. What will be administered or done to the subject?

2. How long will the subject's participation last?

3. To what tests or examinations will the subject be required to submit?

4. Why is the investigation being conducted?

5. Has this particular study been done previously, and, if so, with what results?

6. What inconveniences or discomforts is the subject likely to experience?

7. What risks or hazards can be reasonably anticipated?

8. What steps will be taken to prevent or minimize these risks or hazards?

APPENDIX B

APPLICATION FOR CLINICAL INVESTIGATION PROJECT

(Exempt report, para 7–2*b*, AR 335–15)

1. PRINCIPAL INVESTIGATOR:

2. PROJECT TITLE: (Enter short project title.)

3. OBJECTIVE: (Brief but specific statement of the objective of the project.)

4. MEDICAL APPLICATION: (Explain briefly the medical importance and possible usefulness of the project.)

5. STATUS: (What has been accomplished or published in the proposed area of study and in what manner will the project relate to or differ from that which has been accomplished. If references or personal communication with other Army medical facilities are involved, so indicate.)

6. PLAN: (Outline exactly what is proposed to be accomplished in sufficient detail to indicate a clear course of action. Technological validity of procedures and chronological steps should be shown.) (*Note.* The Surgeon General and the local commander must have a very clear picture of how the investigation will proceed to meet the objective of the project. This paragraph frequently furnishes the basis for approval or disapproval of a project.)

7. BIBLIOGRAPHY: (List sources of information.)

8. FACILITIES TO BE USED: (Such as laboratory, ward, clinic.)

9. TIME REQUIRED TO COMPLETE: (Give month and year of expected start and anticipated completion).

10. PERSONNEL TO CONDUCT PROJECT: (List names and positions of persons to be directly involved in project work.) (Attach short biographical sketch, including resume of education, research training, and list of publications, for each person named.)

11. FUNDING IMPLICATIONS:

	O&MA	*OPA*	*Total*
a. Personnel: (itemize and explain need)	$____	$____	$____
b. Equipment: (itemize and explain need)	$____	$____	$____
c. Consumable Supplies: (itemize)	$____	$____	$____
d. Travel: itemize and explain need)	$____	$____	$____
e. Modification of facilities: (explain)	$____	$____	$____
f. Other (explain)	$____	$____	$____
TOTAL	$____	$____	$____

12. DATE PREPARED: (Give day, month, and year of preparation.)

(Signature of Principal Investigator) (Signature of Department Chief)

(Enter title and mailing address of Principal Investigator)

APPENDIX C

REPORTING GUIDELINES

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  - (1) Manpower
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VIII. INDEX
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- *b.* Author

IX. BACK COVER

The proponent agency of this regulation is the Office of The Surgeon General. Users are invited to send comments and suggested improvements on DA Form 2028 (Recommended Changes to Publications) direct to HQDA (DASG) WASH, DC 20314.

By Order of the Secretary of the Army:

CREIGHTON W. ABRAMS
General, United States Army
Chief of Staff

Official:
VERNE L. BOWERS
Major General, United States Army
The Adjutant General

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USAR: D (Qty Rqr Block No. 107)

TAGO 405A

U.S. GOVERNMENT PRINTING OFFICE: 1979

STATEMENT

BY

LIEUTENANT GENERAL RICHARD R. TAYLOR, M.D.

THE SURGEON GENERAL

DEPARTMENT OF THE ARMY

BEFORE THE

SUBCOMMITTEE ON ADMINISTRATIVE PRACTICE AND PROCEDURE

OF THE

JUDICIARY COMMITTEE

AND THE

SUBCOMMITTEE ON HEALTH OF THE LABOR AND PUBLIC WELFARE COMMITTEE

UNITED STATES SENATE

FIRST SESSION, 94th CONGRESS

10 September 1975

NOT FOR PUBLICATION
UNTIL RELEASED BY THE
SUBCOMMITTEE ON ADMINISTRATIVE
PRACTICE AND PROCEDURE

BIOGRAPHICAL SKETCH OF WITNESS: Lieutenant General Richard R. Taylor, M.D. [redacted] After completing premedical studies at the University of Chicago in 1944; he graduated in 1946 with a doctor of medicine degree.

General Taylor attended the Army Medical Department officer's basic course, after completing an internship at the Highland Alameda County Hospital, Oakland, California, in 1947. His first medical assignment was as a general medical officer at the Army-Navy General Hospital in Hot Springs, Arkansas. After attending the company grade medical officer's course, he completed his residency training at Letterman General Hospital in internal medicine and cardiology.

In 1953, General Taylor was assigned to Korea, first as Assistant Division Surgeon, then as Commander, 7th Medical Battalion, 7th Infantry Division, later serving as an internist at the Hemorrhagic Fever Center, 45th Evacuation Hospital. In 1955, General Taylor returned to the United States as a resident in pulmonary disease at Fitzsimons General Hospital and later became Chief, Non-TB Chest Disease Service.

In 1957, he became Commanding Officer, US Army Medical Research and Development Unit, Fitzsimons General Hospital.

Following a fellowship in tropical medicine at Louisiana State University in 1959, General Taylor became Chief, Biophysics and Astronautics Research Branch of the US Army Medical Research and Development Command. After successive staff assignments, he was named Deputy Commander of the Command in 1963.

September 1964 saw General Taylor serving as Staff Surgeon of the Joint US Military Assistance Group in Thailand and Command Surgeon of the Military Assistance Command, Thailand. After attending the Army War College at Carlisle Barracks, Pennsylvania, he served in the Office of the Secretary of Defense as Chief, Biological and Medical Sciences Division, Office of the Director of Defense Research and Engineering.

He served as Command Surgeon, Headquarters, Military Assistance Command, Vietnam, from 1969-70, where he was promoted to Brigadier General on October 1, 1969. In September 1970, he became Commanding General of the US Army Medical Research and Development Command. He was sworn in as the Deputy Surgeon General on March 1, 1973, and became The Surgeon General, US Army, on October 1, 1973.

He is certified by the American Board of Internal Medicine, and is a Fellow of both the American College of Physicians and the American College of Chest Physicians. He is a member of the American Medical Association, the Association of Military Surgeons of the US (Past President), and the New York Academy of Science.

His awards and decorations include the Distinguished Service Medal, the Legion of Merit with oak leaf cluster, the Bronze Star Medal, the Joint Services Commendation Medal with oak leaf cluster and the Army Commendation Medal with oak leaf cluster.

Mr. Chairman:

I am pleased to appear before you to review Department of Defense policies and procedures to protect the rights and welfare of human subjects of biomedical and behavioral research conducted under its sponsorship. I believe that your invitation was based upon a desire to know whether the Department of Defense has sponsored or is now sponsoring medical research which exposes human beings to unreasonable risks. I refer to the risks of death or likely permanent damage to the mind, personality, or physical well-being as a result of research. I assure you that Department of Defense policy prohibits research carrying this degree of risk as well as research on humans who have not given their free and informed consent. I believe that you also wish to know whether the Department of Defense meets current standards for conduct of research in human subjects. The Department of Defense and the military departments today follow standards for protection of research subjects which equal or exceed those followed by other Federal agencies and the medical community at large.

The basic Department of Defense policy governing medical experiments was promulgated by the Secretary of Defense on 26 February 1953 (Incl 1). This policy is based on the Nuremberg Code of 1947, which followed the war crimes trials (Incl 2). The Chief of Staff published an implementing Memorandum in 1953. The departmental regulations implementing the tightening Federal controls of studies using investigational drugs, use of volunteers in medical research, and clinical investigations are listed at Incl 3. Copies of these regulations are available to your staff.

Some impacts of these various regulations are that an individual participating as a subject is required to be fully informed of the nature, purposes, and the effects of the experimentation; he must give voluntary written informed consent without coercion; and he must be allowed to withdraw at any point from the experiment.

These basic moral, ethical, and legal principles, identified above, are common to the regulations of the military departments. The Department of Defense has demonstrated a continuing concern in this area and has reviewed the procedures and taken corrective action where it was needed.

In 1964, HEW and DOD entered into a Memorandum of Understanding related to new regulatory authority and responsibilities of the FDA concerning investigational drugs. This Memorandum and subsequent DOD Directives and service regulations established Investigational Drug Review Boards within the Offices of the Surgeons General. The boards provide professional review of proposed investigations with new drugs and biologicals. With these boards, the DOD was permitted certain exceptions from ordinary FDA review, including military requirements work which was classified, for reasons of national security. The DOD agreed to discuss its classified investigations of drugs periodically with FDA personnel who had proper security clearance and to report to FDA findings associated with such studies which FDA should be aware of to make a sound evaluation of non-classified studies proposed on the same or similar drugs.

In May 1974, the Army staff responsibility for research involving life sciences was transferred from the Army Research Office, Office of the Chief of Research and Development, to The Surgeon General. In July of 1974, the approval authority for all research involving human subjects in the Army, except for nuclear and chemical warfare related studies, was transferred from the Office of the Chief of Research and Development to The Surgeon General. Proposals for research with nuclear or chemical warfare agents are forwarded by The Surgeon General with recommendations on the medical aspects to the Secretary of the Army for approval.

In October 1974, The Surgeon General established the Human Use Review Office under the direction of the Assistant Surgeon General for Research and Development. The Human Use Review Office was charged with administering and coordinating activities of the Army Investigational Drug Review Board, the US Army Medical Research and Development Command Contract Review Board, and The Surgeon General's Human Use Committee and Clinical Investigation Committee to insure uniform application of ethical standards for human research studies conducted within or sponsored by the Army Medical Department and other Army agencies.

The Human Use Review Committee is the central Army processing point for all extramural and intramural human subjects research which require approval under provisions of Army Regulations. The staff includes a full time physician, two pharmacists with advanced training in pharmacology and a biostatistician. Legal advice is provided by attorneys in the Army Medical Research and Development Command. This medical

scientific, and legal staff identifies problem areas and requests review by expert professional consultants, clarifications and/or revision before protocols are submitted to appropriate committees for review and recommendations to The Surgeon General. The Deputy Surgeon General has been delegated authority for final approval except for nuclear and chemical warfare related studies. The Secretary of the Army retains final approval authority for all studies with nuclear or chemical warfare agents. The Human Use Review Office is the authorized channel through which Army investigators communic: with the Food and Drug Administration (FDA). The Army committees on human subjects research reviewed and made recommendations on over 300 research proposals during fisca. year 1975. Provisions for the protection of human subjects and the detailed content of consent agreements were the primary concern of the members. The careful review is reflected by the fact that a large number of proposals were disapproved or deferred perci revision of the consent procedures. The Human Use Review Office staff and committees apply the standards contained in current Department of Defense and Department of Healt Education, and Welfare (DHEW) regulations. For example, when the recent HEW mora- torium on fetal research was promulgated, the files were searched to be sure such researc was not being conducted within the Army Clinical Investigation Program. The Human Use Review committees have paid particular attention to special classes of subjects involved in Army research i.e. children, pregnant women, and prisoners, and have often required special consent procedures appropriate to a particular project.

Within the Army, increased emphasis has been placed on insuring that agencies outside the Army Medical Department follow the same high standards as those within it. We have insisted that other Army agencies interpret the language of AR 70-25

broadly to include all experiments which may expose participants to risk even thou the project proponents may consider the testing to be primarily an operational exa ination of prototype machinery or equipment. If a test of a new uniform or vehicl for example, may expose subjects to risks from heat stress, noise, or fumes, the protocol is examined in detail to be sure that the subjects are fully informed volun and to reduce risk as much as possible. A large amount of time and effort is often required to adequately review tests of this type since their uniquely military settin sometimes makes it difficult to distinguish clearly what tasks are reasonably "in th line of duty."

Scope of Department of Defense Research Involving Human Subjects

Within this context, I would like to discuss in broad terms the present Depart of Defense research effort involving human subjects. Military missions expose tro to extremely diverse hazards and stresses, including "exotic" infections such as malaria and scrub typhus, great pressure variations, as in deep diving, and crash forces; and high and low velocity missile combat wounds. The effectiveness of ev our most "automated" military systems still is intimately linked to proper human performance. The rising cost of defense manpower means that efforts to decrease non-effectiveness of military personnel are increasingly important. Within our military health care systems we must conserve the fighting strength, and maintain quality health care. It should not be surprising that a defense environment of this kind generates requirements for research and investigation which can only be met t the use of human subjects.

All Department of Defense work using human subjects is conducted to meet requirements of the Department of Defense. There are two main divisions of this work. First, and by far the largest, is the RDTE funded program. The second, and newer program is that of clinical investigations funded in operations and maintenance accounts.

The RDTE program is reviewed by the Director of Defense Research and Engineeri and conducted by the Military Departments. Its requirements are generated by milit unique needs of the Department of Defense and the Military Departments.

The Assistant Secretary of Defense (Health and Environment) is the DOD propone of the clinical investigation program. The requirement for this program is generated by the Department of Defense mission of providing health care and training of medica personnel. The work here more nearly resembles civilian (university) research progra Professional postgraduate medical training requires the experience of research or cli investigation, while the opportunity to participate in clinical investigations remains an important career incentive. While the work may not be unique to the Military Departments, it is usually of considerable relevance and aimed at improving the care in military hospitals.

Some examples of military medical research are:

Casualty Care

a. Use of electrical anesthesia in surgery.

b. Tissue (bone) transplantation in the treatment of severe maxillofacial wound

Infectious Disease. This area is one of great importance and interest in the Department of Defense and accounts for the largest use of human subjects, chiefly in vaccine development.

a. Development and testing of a meningococcal meningitis vaccine to protect recruit populations.

b. Development and testing of new antimalarial drugs against malaria resistant to conventional medications.

Following tests for safety and effectiveness in experimental animals, humans must be involved initially in small and later larger scale tests.

Hazard Protection

Human testing of physiological techniques to improve tolerance to sustained high acceleration forces encountered in combat aircraft.

Evaluation of body heat loss encountered in cold-water diving in various protective suits.

This area of research is primarily performed by active duty military personnel who are skilled in operating in these unusual environments and who have volunteered for hazardous duty, for which they receive extra pay. This area of research is potentially the most hazardous of Department of Defense research and the one with the most highly trained subjects.

Defense Against Chemical Weapons

This research is conducted in service and under contract by Edgewood Arsenal, which is a part of the US Army Materiel Command. Research involving defense against chemical and biological weapons was authorized by the Secretary of the Army in 1953 and has been governed by Department of Defense and Army directives originally written in 1953 containing the language of the Nuremberg Code which I referred to earlier. This work was reviewed in open hearings before the House Committee on Science and Astronautics, 16 and 22 June 1959, and on several later occasions by Congressional Committees. The major research effort is involved with trying to find more effective antidote drugs to counteract chemical weapons that we know are in the arsenals of potential enemies. Many of the drugs that are used do temporarily affect performance and ability to do complex tasks but this is a side effect and not an intended purpose of using the drug. I am sure you may have many questions about the history of this type of research and I will do my best to answer them. I would like to point out, however, that no drug is tested if there is any suspicion from pre-clinical testing in animals that it will have serious adverse or long lasting effects. Furthermore, the review mechanisms applied to Edgewood have been tightened over the last two years so that protocols are reviewed by the Army Investigational Drug Review Board and Human Subjects Research Review Board and relevant Department of Defense and Food and Drug Administration regulations are followed. A case in point is the newly developed antidote called "TAB" which will replace the traditional atropine antidote carried by US Armed Forces. A meeting was held with the FDA in

November 1974 regarding the deployment of this new drug. Since that time, further clinical studies have been postponed pending submission of further data to FDA. Concerns expressed by former participants in the Army Chemical Warfare human testing program on lysergic acid diethylamide (LSD) have prompted me to direct a complete medical follow-up study of all participants. The current status of the follow-up is at Incl 4.

Other Work with Investigational Drugs

There is presently no classified work with investigational drugs being conducted in the Department of Defense. The large majority of this work has always been open and reported fully to the Food and Drug Administration. Presumably all use of investigational drugs in the Department of Defense is formally on file with the FDA and projects are subject to that agency's review before projects are begun. In addition to the 1974 meeting, mentioned above, representatives of the Food and Drug Administration reviewed the medical research activities at Edgewood Arsenal in 1967, pursuant to the HEW/DOD agreement, and a liaison visit by FDA was made to the Biomedical Laboratory, Edgewood Arsenal in 1972. More detailed information about Department of Defense research involving human subjects will be provided for the record. Historical information which you may desire will be promptly retrieved.

As you have heard, there is evidence that the sound ethical principles directed in past and present DOD regulations appear not always to have been followed, particularly in the 1950's. Where this has been true, I believe that the problem has not been lack of guidelines but lack of compliance with them. We all deplore any instances in which the welfare of human subjects was not properly protected.

Procedures have been implemented that tighten control of this work so that the future will not provide more incidents. I assure you that no contract or in service projects calling for experimentation upon human beings will be done in the future by any part of the Department of Defense without the proper safeguards. In addition, action has been taken to insure that any participation in volunteer studies under the sponsorship of Fort Detrick or Edgewood Arsenal by service personnel will be carefully documented in individual medical records.

My aim has been to give you an overview of the subject. I assure you that when we ask people to assume any degree of risk as part of a Department of Defense medical or behavioral research project, we do it in the context of a long tradition of ethical responsibility. I believe our past efforts to protect subjects have been vigorous but we are always striving to improve.

COPY

SECRETARY OF DEFENSE
Washington

26 Feb 1953

MEMORANDUM FOR THE SECRETARY OF THE ARMY
SECRETARY OF THE NAVY
SECRETARY OF THE AIR FORCE

SUBJECT: Use of Human Volunteers in Experimental Research

1. Based upon a recommendation of the Armed Forces Medical Policy Council, that human subjects be employed, under rigid safeguards, as the only feasible means for realistic evaluation and/or development of effective preventive measures of defense against atomic, biological or chemical agents, the policy set forth below will govern the use of human volunteers by the Department of Defense in experimental research in the fields of atomic, biological and/or chemical warfare.

2. By reason of the basic medical responsibility in connection with the development of defense of all types against atomic, biological and/or chemical warfare agents, Armed Services personnel and/or civilians on duty at installations engaged in such research shall be permitted to actively participate in all phases of such program, such participation shall be subject to the following conditions:

a. The voluntary consent of the human subject is absolutely essential.

(1) This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, over-reaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision. This latter element requires that before the acceptance of an affirmative decision by the experimental subject there should be made known to him the nature, duration, and purpose of the experiment; the method and means by

TOP SECRET

COPY

which it is to be conducted; all inconveniences and hazards reasonably to be expected; and the effects upon his health or person which may possibly come from his participation in the experiment.

(2) The concept of the human subject shall be in writing, his signature shall be affixed to a written instument setting forth substantially the aforementioned requirements and shall be signed in the presence of at least one witness who shall attest to such signature in writing.

(a) In experiments where personnel from more than one Service are involved the Secretary of the Service which is exercising primary responsibility for conducting the experiment is designated to prepare such an instrument and coordinate it for use by all the Services having human volunteers involved in the experiment.

(3) The duty and responsibility for ascertaining the quality of the consent rests upon each individual who initiates, directs or engages in the experiment. It is a personal duty and responsibility which may not be delegated to another with impunity.

b. The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature.

c. The number of volunteers used shall be kept at a minimum consistent with item b., above.

d. The experiment should be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problem under study that the anticipated results will justify the performance of the experiment.

e. The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury.

f. No experiment should be conducted where there is an a priori reason to believe that death or disabling injury will occur.

g. The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.

C O P Y

h. Proper preparation should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability, or death.

i. The experiment should be conducted only by scientifically qualified persons. The highest degree of skill and care should be required through all stages of the experiment of those who conduct or engage in the experiment.

j. During the course of the experiment the human subject should be at liberty to bring the experiment to an end if he has reached the physical or mental state where continuation of the experiment seems to him to be impossible.

k. During the course of the experiment the scientist in charge must be prepared to terminate the experiment at any stage if he has probable cause to believe, in the exercise of the good faith, superior skill and careful judgment required of him that continuation of the experiment is likely to result in injury, disability, or death to the experimental subject.

l. The established policy, which prohibits the use of prisoners of war in human experimentation, is continued and they will not be used under any circumstances.

3. The Secretaries of the Army, Navy and Air Force are authorized to conduct experiments in connection with the development of defenses of all types against atomic, biological and/or chemical warfare agents involving the use of human subjects within the limits prescribed above.

4. In each instance in which an experiment is proposed pursuant to this memorandum, the nature and purpose of the proposed experiment and the name of the person who will be in charge of such experiment shall be submitted for approval to the Secretary of the military department in which the proposed experiment is to be conducted. No such experiment shall be undertaken until such Secretary has approved in writing the experiment proposed, the person who will be in charge of conducting it, as well as informing the Secretary of Defense.

5. The addressees will be responsible for insuring compliance with the provisions of this memorandum within their respective Services.

/signed/
C.E. WILSON

Copies furnished:
Joint Chiefs of Staff
Research and Development Board

NUREMBERG CODE*

1. The voluntary consent of the human subject is absolutely essential.

This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, over-reaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision. This latter element requires that before the acceptance of an affirmative decision by the experimental subject there should be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonably to be expected; and the effects upon his health or person which may possibly come from his participation in the experiment.

The duty and responsibility for ascertaining the quality of the consent rests upon each individual who initiates, directs, or engages in the experiment. It is a personal duty and responsibility which may not be delegated to another with impunity.

2. The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature.

3. The experiment should be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problem under study that the anticipated results will justify the performance of the experiment.

4. The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury.

5. No experiment should be conducted where there is an *a priori* reason to believe that death or disabling injury will occur; except, perhaps, in those experiments where the experimental physicians also serve as subjects.

6. The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.

Proper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability, or death.

8. The experiment should be conducted only by scientifically qualified persons. The highest degree of skill and care should be required through all stages of the experiment of those who conduct or engage in the experiment.

9. During the course of the experiment the human subject should be at liberty to bring the experiment to an end if he has reached the physical or mental state where continuation of the experiment seems to him to be impossible.

10. During the course of the experiment the scientist in charge must be prepared to terminate the experiment at any stage, if he has probable cause to believe, in the exercise of the good faith, superior skill, and careful judgment required of him that a continuation of the experiment is likely to result in injury, disabi-

*Copied from Experimentation with Human Beings by Jay Katz, Russell Sage Foundation, New York 1972.

CURRENT REGULATIONS

Army

AR 40-7	Use of Investigational Drugs in Humans and the Use of Schedule I Controlled Drug Substances, 4 Apr 75
AR 40-38	Clinical Investigation Program, 23 Feb 73
AR 70-25	Use of Volunteers as Subjects of Research, 15 Sep 74

Navy

BUMEDINST 6000.4B	Clinical Investigation Program, 15 Jan 75
BUMEDINST 6710.49D	Investigational Use of New Drugs in Human Beings, 9 Jul 73
SECNAVINST 3900.39	Use of Volunteers as Subjects in Research, Development, Test and Evaluation, 28 Apr 69

Air Force

AFR 169-6	Clinical Investigation, 26 Jun 74
AFR 169-8	Use of Human Test Subjects in the Medical Service, 19 Aug 74
AFR 80-33	Use of Volunteers in Aerospace Research, 28 Aug 69

INFORMATION PAPER

SGRD-UR
9 September 1975

SUBJECT: Progress on Followup of Subjects of LSD and Other Army Psychoactive Drug Research

FACTS.

1. List of LSD subjects has been collated from Edgewood Arsenal records and also from The Inspector General records. List contains 320 names, some of which were added sporadically over the last several weeks since Edgewood records are incomplete prior to 1961.

2. Representatives of the Surgeon General traveled to St. Louis Records Center 25-29 August 1975. Center was able to provide Social Security Account Numbers and old addresses on 209 persons. Rest of group were not found there either because of destruction of records by fire or inadequacy of computer to locate file from information (service number) available.

3. Other data bases to be used are Veterans Administration (VA) files and Social Security files. National Academy of Sciences Medical Followup Agency has extensive experience using these data bases. LSD Followup Task Force is planning details of proposal for followup examinations to be submitted to the National Academy of Sciences.

4. Nineteen of the Fort Benning group have been examined at Walter Reed Army Medical Center. Of this group, one man, in addition to LTC Jordan, had an abnormal EEG. Consultants at Walter Reed Army Medical Center do not feel that LSD was originally associated with this abnormality.

5. Several men from the Fort Benning group who originally declined examination were reconnected but declined again. The seven men who could not be reached have been sent letters through the Social Security Account Number system.

SGRD-HR

SUBJECT: Progress on Followup of Subjects of LSD and Other Army Psychoactive Drug Research

6. In the last seven weeks, 113 persons have inquired at the Office of The Surgeon General about drug testing. Twenty-six were on record as having taken LSD and were notified that they would be examined. Approximately 30 took other drugs at Edgewood Arsenal, Maryland, and their request for information have been handled appropriately.

7. A systematic analysis will be made of drug studies performed at Edgewood to determine which subjects of tests not involving LSD require followup.

MAJ Johnston/[illegible]

OPRR Reports

NIH PHS HHS

The Belmont Report

Ethical Principles and Guidelines for the Protection of Human Subjects of Research

The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research

April 18, 1979

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Office of the Secretary

Protection of Human Subjects

Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, Report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research

AGENCY: Department of Health, Education, and Welfare.

ACTION: Notice of Report for Public Comment.

SUMMARY: On July 12, 1974, the National Research Act (Pub. L. 93-348) was signed into law, there-by creating the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. One of the charges to the Commission was to identify the basic ethical principles that should underlie the conduct of biomedical and behavioral research involving human subjects and to develop guidelines which should be followed to assure that such research is conducted in accordance with those principles. In carrying out the above, the Commission was directed to consider: (i) the boundaries between biomedical and behavioral research and the accepted and routine practice of medicine, (ii) the role of assessment of risk-benefit criteria in the determination of the appropriateness of research involving human subjects, (iii) appropriate guidelines for the selection of human subjects for participation in such research and (iv) the nature and definition of informed consent in various research settings.

The Belmont Report attempts to summarize the basic ethical principles identified by the Commission in the course of its deliberations. It is the outgrowth of an intensive four-day period of discussions that were held in February 1976 at the Smithsonian Institution's Belmont Conference Center supplemented by the monthly deliberations of the Commission that were held over a period of nearly four years. It is a statement of basic ethical principles and guidelines that should assist in resolving the ethical problems that surround the conduct of research with human subjects. By publishing the Report in the **Federal Register**, and providing reprints upon request, the Secretary intends that it may be made readily available to scientists, members of Institutional Review Boards, and Federal employees. The two-volume Appendix, containing the lengthy reports of experts and specialists who assisted the Commission in fulfilling this part of its charge, is available as DHEW Publication No. (OS) 78–0013 and No. (OS) 78–0014, for sale by the Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402.

Unlike most other reports of the Commission, the Belmont Report does not make specific recommendations for administrative action by the Secretary of Health, Education, and Welfare. Rather, the Commission recommended that the Belmont Report be adopted in its entirety, as a statement of the Department's policy. The Department requests public comment on this recommendation.

National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research

Members of the Commission

Kenneth John Ryan, M.D., Chairman, Chief of Staff, Boston Hospital for Women.

Joseph V. Brady, Ph.D., Professor of Behavioral Biology, Johns Hopkins University.

Robert E. Cooke, M.D., President, Medical College of Pennsylvania.

Dorothy I. Height, President, National Council of Negro Women, Inc.

Albert R. Jonsen, Ph.D., Associate Professor of Bioethics, University of California at San Francisco.

Patricia King, J.D., Associate Professor of Law, Georgetown University Law Center.

Karen Lebacqz, Ph.D., Associate Professor of Christian Ethics, Pacific School of Religion.

*David W. Louisell, J.D., Professor of Law, University of California at Berkeley.

Donald W. Seldin, M.D., Professor and Chairman, Department of Internal Medicine, University of Texas at Dallas.

Eliot Stellar, Ph.D., Provost of the University and Professor of Physiological Psychology, University of Pennsylvania.

*Robert H. Turtle, LL.B., Attorney, VomBaur, Coburn, Simmons & Turtle, Washington, D.C.

*Deceased.

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Belmont Report

Ethical Principles and Guidelines for Research Involving Human Subjects

Scientific research has produced substantial social benefits. It has also posed some troubling ethical questions. Public attention was drawn to these questions by reported abuses of human subjects in biomedical experiments, especially during the Second World War. During the Nuremberg War Crime Trials, the Nuremberg code was drafted as a set of standards for judging physicians and scientists who had conducted biomedical experiments on concentration camp prisoners. This code became the prototype of many later codes[1] intended to assure that research involving human subjects would be carried out in an ethical manner.

The codes consist of rules, some general, others specific, that guide the investigators or the reviewers of research in their work. Such rules often are inadequate to cover complex situations; at times they come into conflict, and they are frequently difficult to interpret or apply. Broader ethical principles will provide a basis on which specific rules may be formulated, criticized and interpreted.

Three principles, or general prescriptive judgments, that are relevant to research involving human subjects are identified in this statement. Other principles may also be relevant. These three are comprehensive, however, and are stated at a level of generalization that should assist scientists, subjects, reviewers and interested citizens to understand the ethical issues inherent in research involving human subjects. These principles cannot always be applied so as to resolve beyond dispute particular ethical problems. The objective is to provide an analytical framework that will guide the resolution of ethical problems arising from research involving human subjects.

This statement consists of a distinction between research and practice, a discussion of the three basic ethical principles, and remarks about the application of these principles.

A. Boundaries Between Practice and Research

It is important to distinguish between biomedical and behavioral research, on the one hand, and the practice of accepted therapy on the other, in order to know what activities ought to undergo review for the protection of human subjects of research. The distinction between research and practice is blurred partly because both often occur together (as in research designed to evaluate a therapy) and partly because notable departures from standard practice are often called "experimental" when the terms "experimental" and "research" are not carefully defined.

For the most part, the term "practice" refers to interventions that are designed solely to enhance the well-being of an individual patient or client and that have a reasonable expectation of success. The purpose of medical or behavioral practice is to provide diagnosis, preventive treatment or therapy to particular individuals.[2] By contrast, the term "research" designates an activity designed to test an hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge (expressed, for example, in theories, principles, and statements of relationships). Research is usually described in a formal protocol that sets forth an objective and a set of procedures designed to reach that objective.

When a clinician departs in a significant way from standard or accepted practice, the innovation does not, in and of itself, constitute research. The fact that a procedure is "experimental," in the sense of new, untested or different, does not automatically place it in the category of research. Radically new procedures of this description should, however, be made the object of formal research at an early stage in order to determine whether they are safe and effective. Thus, it is the responsibility of medical practice committees, for example, to insist that a major innovation be incorporated into a formal research project.[3]

Research and practice may be carried on together when research is designed to evaluate the safety and efficacy of a therapy. This need not cause any confusion regarding whether or not the activity requires review; the general rule is that if there is any element of research in an activity, that activity should undergo review for the protection of human subjects.

B. Basic Ethical Principles

The expression "basic ethical principles" refers to those general judgments that serve as a basic justification for the many particular ethical prescriptions and evaluations of

[1] Since 1945, various codes for the proper and responsible conduct of human experimentation in medical research have been adopted by different organizations. The best known of these codes are the Nuremberg Code of 1947, the Helsinki Declaration of 1964 (revised in 1975), and the 1971 Guidelines (codified into Federal Regulations in 1974) issued by the U.S. Department of Health, Education, and Welfare Codes for the conduct of social and behavioral research have also been adopted, the best known being that of the American Psychological Association, published in 1973.

[2] Although practice usually involves interventions designed solely to enhance the well-being of a particular individual, interventions are sometimes applied to one individual for the enhancement of the well-being of another (e.g., blood donation, skin grafts, organ transplants) or an intervention may have the dual purpose of enhancing the well-being of a particular individual, and, at the same time, providing some benefit to others (e.g., vaccination, which protects both the person who is vaccinated and society generally). The fact that some forms of pratice have elements other than immediate benefit to the individual receiving an intervention, however, should not confuse the general distinction between research and practice. Even when a procedure applied in practice may benefit some other person, it remains an intervention designed to enhance the well-being of a particular individual or groups of individuals; thus, it is practice and need not be reviewed as research.

[3] Because the problems related to social experimentation may differ substantially from those of biomedical and behavioral research, the Commission specifically declines to make any policy determination regarding such research at this time. Rather, the Commission believes that the problem ought to be addressed by one of its successor bodies.

human actions. Three basic principles, among those generally accepted in our cultural tradition, are particularly relevant to the ethics of research involving human subjects: the principles of respect for persons, beneficence and justice.

1. *Respect for Persons.*—Respect for persons incorporates at least two ethical convictions: first, that individuals should be treated as autonomous agents, and second, that persons with diminished autonomy are entitled to protection. The principle of respect for persons thus divides into two separate moral requirements: the requirement to acknowledge autonomy and the requirement to protect those with diminished autonomy.

An autonomous person is an individual capable of deliberation about personal goals and of acting under the direction of such deliberation. To respect autonomy is to give weight to autonomous persons' considered opinions and choices while refraining from obstructing their actions unless they are clearly detrimental to others. To show lack of respect for an autonomous agent is to repudiate that person's considered judgments, to deny an individual the freedom to act on those considered judgments, or to withhold information necessary to make a considered judgment, when there are no compelling reasons to do so.

However, not every human being is capable of self-determination. The capacity for self-determination matures during an individual's life, and some individuals lose this capacity wholly or in part because of illness, mental disability, or circumstances that severely restrict liberty. Respect for the immature and the incapacitated may require protecting them as they mature or while they are incapacitated.

Some persons are in need of extensive protection, even to the point of excluding them from activities which may harm them; other persons require little protection beyond making sure they undertake activities freely and with awareness of possible adverse consequences. The extent of protection afforded should depend upon the risk of harm and the likelihood of benefit. The judgment that any individual lacks autonomy should be periodically reevaluated and will vary in different situations.

In most cases of research involving human subjects, respect for persons demands that subjects enter into the research voluntarily and with adequate information. In some situations, however, application of the principle is not obvious. The involvement of prisoners as subjects of research provides an instructive example. On the one hand, it would seem that the principle of respect for persons requires that prisoners not be deprived of the opportunity to volunteer for research. On the other hand, under prison conditions they may be subtly coerced or unduly influenced to engage in research activities for which they would not otherwise volunteer. Respect for persons would then dictate that prisoners be protected. Whether to allow prisoners to "volunteer" or to "protect" them presents a dilemma. Respecting persons, in most hard cases, is often a matter of balancing competing claims urged by the principle of respect itself.

2. *Beneficence.*—Persons are treated in an ethical manner not only by respecting their decisions and protecting them from harm, but also by making efforts to secure their well-being. Such treatment falls under the principle of beneficence. The term "beneficence" is often understood to cover acts of kindness or charity that go beyond strict obligation. In this document, beneficence is understood in a stronger sense, as an obligation. Two general rules have been formulated as complementary expressions of beneficent actions in this sense: (1) do not harm and (2) maximize possible benefits and minimize possible harms.

The Hippocratic maxim "do no harm" has long been a fundamental principle of medical ethics. Claude Bernard extended it to the realm of research, saying that one should not injure one person regardless of the benefits that might come to others. However, even avoiding harm requires learning what is harmful; and, in the process of obtaining this information, persons may be exposed to risk of harm. Further, the Hippocratic Oath requires physicians to benefit their patients "according to their best judgment." Learning what will in fact benefit may require exposing persons to risk. The problem posed by these imperatives is to decide when it is justifiable to seek certain benefits despite the risks involved, and when the benefits should be foregone because of the risks.

The obligations of beneficence affect both individual investigators and society at large, because they extend both to particular research projects and to the entire enterprise of research. In the case of particular projects, investigators and members of their institutions are obliged to give forethought to the maximization of benefits and the reduction of risk that might occur from the research investigation. In the case of scientific research in general, members of the larger society are obliged to recognize the longer term benefits and risks that may result from the improvement of knowledge and from the development of novel medical, psychotherapeutic, and social procedures.

The principle of beneficence often occupies a well-defined justifying role in many areas of research involving human subjects. An example is found in research involving children. Effective ways of treating childhood diseases and fostering healthy development are benefits that serve to justify research involving children—even when individual research subjects are not direct beneficiaries. Research also makes is possible to avoid the harm that may result from the application of previously accepted routine practices that on closer investigation turn out to be dangerous. But the role of the principle of beneficence is not always so unambiguous. A difficult ethical problem remains, for example, about research that pres-

ents more than minimal risk without immediate prospect of direct benefit to the children involved. Some have argued that such research is inadmissible, while others have pointed out that this limit would rule out much research promising great benefit to children in the future. Here again, as with all hard cases, the different claims covered by the principle of beneficence may come into conflict and force difficult choices.

3. *Justice.*—Who ought to receive the benefits of research and bear its burdens? This is a question of justice, in the sense of "fairness in distribution" or "what is deserved." An injustice occurs when some benefit to which a person is entitled is denied without good reason or when some burden is imposed unduly. Another way of conceiving the principle of justice is that equals ought to be treated equally. However, this statement requires explication. Who is equal and who is unequal? What considerations justify departure from equal distribution? Almost all commentators allow that distinctions based on experience, age, deprivation, competence, merit and position do sometimes constitute criteria justifying differential treatment for certain purposes. It is necessary, then, to explain in what respects people should be treated equally. There are several widely accepted formulations of just ways to distribute burdens and benefits. Each formulation mentions some relevant property on the basis of which burdens and benefits should be distributed. These formulations are (1) to each person an equal share, (2) to each person according to individual need, (3) to each person according to individual effort, (4) to each person according to societal contribution, and (5) to each person according to merit.

Questions of justice have long been associated with social practices such as punishment, taxation and political representation. Until recently these questions have not generally been associated with scientific research. However, they are foreshadowed even in the earliest reflections on the ethics of research involving human subjects. For example, during the 19th and early 20th centuries the burdens of serving as research subjects fell largely upon poor ward patients, while the benefits of improved medical care flowed primarily to private patients. Subsequently, the exploitation of unwilling prisoners as research subjects in Nazi concentration camps was condemned as a particularly flagrant injustice. In this country, in the 1940's, the Tuskegee syphilis study used disadvantaged, rural black men to study the untreated course of a disease that is by no means confined to that population. These subjects were deprived of demonstrably effective treatment in order not to interrupt the project, long after such treatment became generally available.

Against this historical background, it can be seen how conceptions of justice are relevant to research involving human subjects. For example, the selection of research subjects needs to be scrutinized in order to determine whether some classes (e.g., welfare patients, particular racial and ethnic minorities, or persons confined to institutions) are being systematically selected simply because of their easy availability, their compromised position, or their manipulability, rather than for reasons directly related to the problem being studied. Finally, whenever research supported by public funds leads to the development of therapeutic devices and procedures, justice demands both that these not provide advantages only to those who can afford them and that such research should not unduly involve persons from groups unlikely to be among the beneficiaries of subsequent applications of the research.

C. Applications

Applications of the general principles to the conduct of research leads to consideration of the following requirements: informed consent, risk/benefit assessment, and the selection of subjects of research.

1. *Informed Consent.*—Respect for persons requires that subjects, to the degree that they are capable, be given the opportunity to choose what shall or shall not happen to them. This opportunity is provided when adequate standards for informed consent are satisfied.

While the importance of informed consent is unquestioned, controversy prevails over the nature and possibility of an informed consent. Nonetheless, there is widespread agreement that the consent process can be analyzed as containing three elements: information, comprehension and voluntariness.

Information. Most codes of research establish specific items for disclosure intended to assure that subjects are given sufficient information. These items generally include: the research procedure, their purposes, risks and anticipated benefits, alternative procedures (where therapy is involved), and a statement offering the subject the opportunity to ask questions and to withdraw at any time from the research. Additional items have been proposed, including how subjects are selected, the person responsible for the research, etc.

However, a simple listing of items does not answer the question of what the standard should be for judging how much and what sort of information should be provided. One standard frequently invoked in medical practice, namely the information commonly provided by practitioners in the field or in the locale, is inadequate since research takes place precisely when a common understanding does not exist. Another standard, currently popular in malpractice law, requires the practitioner to reveal the information that reasonable persons would wish to know in order to make a decision regarding their care. This, too, seems insufficient since the research subject, being in essence a volunteer, may wish to know considerably more about risks gratuitously undertaken than do patients who deliver themselves into the hand of a clinician for needed care. It may be that a standard of "the reasonable volunteer" should be proposed: the

extent and nature of information should be such that persons, knowing that the procedure is neither necessary for their care nor perhaps fully understood, can decide whether they wish to participate in the furthering of knowledge. Even when some direct benefit to them is anticipated, the subjects should understand clearly the range of risk and the voluntary nature of participation.

A special problem of consent arises where informing subjects of some pertinent aspect of the research is likely to impair the validity of the research. In many cases, it is sufficient to indicate to subjects that they are being invited to participate in research of which some features will not be revealed until the research is concluded. In all cases of research involving incomplete disclosure, such research is justified only if it is clear that (1) incomplete disclosure is truly necessary to accomplish the goals of the research, (2) there are no undisclosed risks to subjects that are more than minimal, and (3) there is an adequate plan for debriefing subjects, when appropriate, and for dissemination of research results to them. Information about risks should never be withheld for the purpose of eliciting the cooperation of subjects, and truthful answers should always be given to direct questions about the research. Care should be taken to distinguish cases in which disclosure would destroy or invalidate the research from cases in which disclosure would simply inconvenience the investigator.

Comprehension. The manner and context in which information is conveyed is as important as the information itself. For example, presenting information in a disorganized and rapid fashion, allowing too little time for consideration or curtailing opportunities for questioning, all may adversely affect a subject's ability to make an informed choice.

Because the subject's ability to understand is a function of intelligence, rationality, maturity and language, it is necessary to adapt the presentation of the information to the subject's capacities. Investigators are responsible for ascertaining that the subject has comprehended the information. While there is always an obligation to ascertain that the information about risk to subjects is complete and adequately comprehended, when the risks are more serious, that obligation increases. On occasion, it may be suitable to give some oral or written tests of comprehension.

Special provision may need to be made when comprehension is severely limited—for example, by conditions of immaturity or mental disability. Each class of subjects that one might consider as incompetent (e.g., infants and young children, mentally disabled patients, the terminally ill and the comatose) should be considered on its own terms. Even for these persons, however, respect requires giving them the opportunity to choose to the extent they are able, whether or not to participate in research. The objections of these subjects to involvement should be honored, unless the research entails providing them a therapy unavailable elsewhere. Respect for persons also requires seeking the permission of other parties in order to protect the subjects from harm. Such persons are thus respected both by acknowledging their own wishes and by the use of third parties to protect them from harm.

The third parties chosen should be those who are most likely to understand the incompetent subject's situation and to act in that person's best interest. The person authorized to act on behalf of the subject should be given an opportunity to observe the research as it proceeds in order to be able to withdraw the subject from the research, if such action appears in the subject's best interest.

Voluntariness. An agreement to participate in research constitutes a valid consent only if voluntarily given. This element of informed consent requires conditions free of coercion and undue influence. Coercion occurs when an overt threat of harm is intentionally presented by one person to another in order to obtain compliance. Undue influence, by contrast, occurs through an offer of an excessive, unwarranted, inappropriate or improper reward or other overture in order to obtain compliance. Also, inducements that would ordinarily be acceptable may become undue influences if the subject is especially vulnerable.

Unjustifiable pressures usually occur when persons in positions of authority or commanding influence—especially where possible sanctions are involved—urge a course of action for a subject. A continuum of such influencing factors exists, however, and it is impossible to state precisely where justifiable persuasion ends and undue influence begins. But undue influence would include actions such as manipulating a person's choice through the controlling influence of a close relative and threatening to withdraw health services to which an individual would otherwise be entitled.

2. Assessment of Risks and Benefits.—The assessment of risks and benefits requires a careful arrayal of relevant data, including, in some cases, alternative ways of obtaining the benefits sought in the research. Thus, the assessment presents both an opportunity and a responsibility to gather systematic and comprehensive information about proposed research. For the investigator, it is a means to examine whether the proposed research is properly designed. For a review committee, it is a method for determining whether the risks that will be presented to subjects are justified. For prospective subjects, the assessment will assist the determination whether or not to participate.

The Nature and Scope of Risks and Benefits. The requirement that research be justified on the basis of a favorable risk/benefit assessment bears a close relation to the principle of beneficence, just as the moral requirement that informed consent be obtained is derived primarily from the principle of respect for persons.

The term "risk" refers to a possibility that harm may occur. However, when expressions such as "small risk" or "high risk" are used, they usually refer (often ambiguously) both to the chance (probability) of experiencing a harm and the severity (magnitude) of the envisioned harm.

The term "benefit" is used in the research context to refer to something of positive value related to health or welfare. Unlike "risk," "benefit" is not a term that expresses probabilities. Risk is properly contrasted to probability of benefits, and benefits are properly contrasted with harms rather than risks of harm. Accordingly, so-called risk/benefit assessments are concerned with the probabilities and magnitudes of possible harms and anticipated benefits. Many kinds of possible harms and benefits need to be taken into account. There are, for example, risks of psychological harm, physical harm, legal harm, social harm and economic harm and the corresponding benefits. While the most likely types of harms to research subjects are those of psychological or physical pain or injury, other possible kinds should not be overlooked.

Risks and benefits of research may affect the individual subjects, the families of the individual subjects, and society at large (or special groups of subjects in society). Previous codes and Federal regulations have required that risks to subjects be outweighed by the sum of both the anticipated benefit to the subject, if any, and the anticipated benefit to society in the form of knowledge to be gained from the research. In balancing these different elements, the risks and benefits affecting the immediate research subject will normally carry special weight. On the other hand, interests other than those of the subject may on some occasions be sufficient by themselves to justify the risks involved in the research, so long as the subjects' rights have been protected. Beneficence thus requires that we protect against risk of harm to subjects and also that we be concerned about the loss of the substantial benefits that might be gained from research.

The Systematic Assessment of Risks and Benefits. It is commonly said that benefits and risks must be "balanced" and shown to be "in a favorable ratio." The metaphorical character of these terms draws attention to the difficulty of making precise judgments. Only on rare occasions will quantitative techniques be available for the scrutiny of research protocols. However, the idea of systematic, nonarbitrary analysis of risks and benefits should be emulated insofar as possible. This ideal requires those making decisions about the justifiability of research to be thorough in the accumulation and assessment of information about all aspects of the research, and to consider alternatives systematically. This procedure renders the assessment of research more rigorous and precise, while making communication between review board members and investigators less subject to misinterpretation, misinformation and conflicting judgments. Thus, there should first be a determination of the validity of the presuppositions of the research; then the nature, probability and magnitude of risk should be distinguished with as much clarity as possible. The method of ascertaining risks should be explicit, especially where there is no alternative to the use of such vague categories as small or slight risk. It should also be determined whether an investigator's estimates of the probability of harm or benefits are reasonable, as judged by known facts or other available studies.

Finally, assessment of the justifiability of research shoud reflect at least the following considerations: (i) Brutal or inhumane treatment of human subjects is never morally justified. (ii) Risks should be reduced to those necessary to achieve the research objective. It should be determined whether it is in fact necessary to use human subjects at all. Risk can perhaps never be entirely eliminated, but it can often be reduced by careful attention to alternative procedures. (iii) When research involves significant risk of serious impairment, review committees should be extraordinarily insistent on the justification of the risk (looking usually to the likelihood of benefit to the subject—or, in some rare cases, to the manifest voluntariness of the participation). (iv) When vulnerable populations are involved in research, the appropriateness of involving them should itself be demonstrated. A number of variables go into such judgments, including the nature and degree of risk, the condition of the particular population involved, and the nature and level of the anticipated benefits. (v) Relevant risks and benefits must be thoroughly arrayed in documents and procedures used in the informed consent process.

3. Selection of Subjects.—Just as the principle of respect for persons finds expression in the requirements for consent, and the principle of beneficence in risk/benefit assessment, the principle of justice gives rise to moral requirements that there be fair procedures and outcomes in the selection of research subjects.

Justice is relevant to the selection of subjects of research at two levels: the social and the individual. Individual justice in the selection of subjects would require that researchers exhibit fairness: thus, they should not offer potentially beneficial research only to some patients who are in their favor or select only "undesirable" persons for risky research. Social justice requires that distinction be drawn between classes of subjects that ought, and ought not, to participate in any particular kind of research, based on the ability of members of that class to bear burdens and on the appropriateness of placing further burdens on already burdened persons. Thus, it can be considered a matter of social justice that there is an order of preference in the selection of classes of subjects (e.g., adults before children) and that some classes of potential subjects (e.g., the institutionalized mentally infirm or prisoners) may be involved as research subjects, if at all, only on certain conditions.

Injustice may appear in the selection of subjects, even if individual subjects are selected fairly by investigators and treated fairly in the course of research. Thus injustice arises from social, racial, sexual and cultural biases institutionalized in society. Thus, even if individual researchers are treating their research subjects fairly, and even if IRBs are taking care to assure that subjects are selected fairly within a particular institution, unjust social patterns may nevertheless appear in the overall distribution of the burdens and benefits of research. Although individual institutions or investigators may not be able to resolve a problem that is pervasive in their social setting, they can consider distributive justice in selecting research subjects.

Some populations, especially institutionalized ones, are already burdened in many ways by their infirmities and environments. When research is proposed that involves risks and does not include a therapeutic component, other less burdened classes of persons should be called upon first to accept these risks of research, except where the research is directly related to the specific conditions of the class involved. Also, even though public funds for research may often flow in the same directions as public funds for health care, it seems unfair that populations dependent on public health care constitute a pool of preferred research subjects if more advantaged populations are likely to be the recipients of the benefits.

One special instance of injustice results from the involvement of vulnerable subjects. Certain groups, such as racial minorities, the economically disadvantaged, the very sick, and the institutionalized may continually be sought as research subjects, owing to their ready availability in settings where research is conducted. Given their dependent status and their frequently compromised capacity for free consent, they should be protected against the danger of being involved in research solely for administrative convenience, or because they are easy to manipulate as a result of their illness or socioeconomic condition.

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(d) Restrictions on Experimentation. Foreign intelligence agencies shall not engage in experimentation with drugs on human subjects, except with the informed consent, in writing and witnessed by a disinterested third party, of each such human subject and in accordance with the guidelines issued by the National Commission for the Protection of Human Subjects for Biomedical and Behavioral Research.

(e) Assistance to Law Enforcement Authorities.

(1) No foreign intelligence agency shall, except as expressly authorized by law (i) provide services, equipment, personnel or facilities to the Law Enforcement Assistance Administration or to State or local police organizations of the United States or (ii) participate in or fund any law enforcement activity within the United States.

(2) These prohibitions shall not, however, preclude: (i) cooperation between a foreign intelligence agency and appropriate law enforcement agencies for the purpose of protecting the personnel and facilities of the foreign intelligence agency or preventing espionage or other criminal activity related to foreign intelligence or counterintelligence or (ii) provision of specialized equipment or technical knowledge for use by any other Federal department or agency.

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UNIVERSITY OF CALIFORNIA CASE STUDY

This case study is an attempt to provide a context for some of the human radiation experiments that were carried out at one part of one institution--the Bay Area campuses of the University of California--and thus to explain not only how but also why such experiments occurred. The focus here is deliberately narrow, upon the exceptional rather than the routine. Throughout, attention centers on a handful of individuals identified as having had a part in those human radiation experiments--the plutonium injections, for example--that were of early and particular interest to the Advisory Committee. Accordingly, the experiments described in this case study should not be considered representative of the broad work of the University of California or its physicians and researchers.

The decision to focus on this particular university was not only a consequence of its central importance in the story of human radiation experiments, but likewise a reflection of the rich documentation surviving in university archives, which makes it possible to tell the story in such detail. In this regard, the University of California has provided great cooperation and assistance to the Advisory Committee in locating the documents that are the basis for this case study.

OVERVIEW

The University of California (UC) has been a pioneer in two distinct but related areas of interest to the Advisory Committee: the development of nuclear medicine, and cooperative arrangements between a major university and the U.S. government in time of national emergency, with the intent of harnessing "science in service of the state."

Several themes emerge from this study. Perhaps most prominent is the way in which biomedical research, having been voluntarily subordinated to the military's needs during the wartime emergency, continued to be dependent upon government support after hostilities had ended and throughout the ensuing Cold War. Prior to Pearl Harbor, much of the funding at the University for both basic science and for applied biomedical research, particularly in the treatment of cancer, was dependent upon the support of a few large, private philanthropic organizations. After the war, not only the funding but also the tools for biomedical research--including permission to use the radioisotopes that became part of the

armamentarium of nuclear medicine--came from a centralized federal bureaucracy, the Atomic Energy Commission (AEC), which had as a part of its charter the active promotion of the benefits of the peaceful atom.

A related theme is the way in which secrecy persisted after the war. Private support for nuclear medicine in the 1930s brought rapid progress, but the imposition of the wartime emergency temporarily redirected efforts in this area and, perhaps more importantly, added an overlay of concern with secrecy that had not existed before. Originally viewed by many in academia as a regrettable if unavoidable exigency of the war, secrecy ultimately became second nature to many researchers. At UC, as in the government generally, the strictures of "need to know" inevitably created opportunities for abuse. Ironically, this sometimes meant that those highest in the hierarchy, and vested with the greatest responsibility, were among the least knowledgeable about what was being done at lower levels. For example, neither UC President Robert Sproul, nor Secretary-Treasurer of the Regents Robert Underhill, was informed of the actual purpose of the Los Alamos project until well after the University had agreed to oversee the project and it was already underway. [1]

Secrecy also meant that claims of national security could be used to classify information that might have been merely embarrassing, or that could have implicated individuals engaged in questionable behavior. Thus, as shown by written instructions issued by the Army in the wake of the plutonium injections controversy, the federal government explicitly extended the cloak of secrecy to include any reference to human experiments which "might have adverse effects on public opinion or result in legal suits."[2] Documents pertaining to government-supported human radiation experiments at UC indicate that representatives of the Army or the AEC, rather than UC researchers, were the ones insisting that human radiation experiments remain secret.

A third theme concerns the diffusion of responsibility for the work that was done, and the impact this had on oversight. In part, this was an unavoidable result of the phenomenal growth of biomedical research involving radiation during and after the war. But, the familiar problems associated with being ruled by two masters--the university and the government, which was now funding much of this research--also created unique problems of oversight. Researchers were able to take advantage of unclear lines of authority, as well as secrecy, not only to short-cut bureaucratic obstacles but also to avoid meaningful supervision. Both the documentary record and anecdotal evidence suggest that universities under contract to the Army, and later the AEC, enjoyed a surprising degree of autonomy in their work. This may have been even more the case with the University of California, where a protracted dispute between the Medical School in San Francisco and the Division of Medical Physics at Berkeley--fought, in part, over the issue of whether human subject research would take place on the Berkeley campus--further clouded the already confused picture of oversight.

A final and very important theme, proceeding from the above, concerns the difficulty of distinguishing between clinical treatment of patients, done for direct therapeutic benefit, and "clinical testing," the term used by the AEC to describe medical research involving human subjects. As the term suggests, clinical testing was presumably done with the intent to provide information for developing future therapies. However, information obtained from government-supported clinical testing was frequently also of military interest, and was consequently ordered classified. The further fact that the funding as well as the radioisotopes for clinical testing were usually obtained from the same source--initially the Army, later the AEC--make it difficult to sort out the mix of motives behind experiments conducted with multiple aims in mind.

PREWAR HISTORY, 1935-1941

The use of artificially produced radioisotopes in the investigation and treatment of disease traces its earliest origins to March 1936, when two UC physician-researchers, Drs. Joseph Hamilton and Robert Stone, tracked the course of radiosodium through the bodies of three volunteer leukemia patients. In December 1937, Dr. John Lawrence--brother of the founder of Berkeley's Radiation Laboratory, Ernest Lawrence--became the first physician to use radiophosphorus for the treatment of leukemia, an application that was extended the following year to the treatment of polycythemia vera. Also in 1938, John Lawrence and Stone pioneered in the use of cyclotron-produced neutrons for the treatment of cancer in humans.[3]

Hamilton and John Lawrence both held joint appointments at UC Medical School in San Francisco (UCSF)--where they were members of the teaching faculty, but did not have a clinical practice--and at Berkeley's Radiation Laboratory.[4] A number of UCSF physicians--preeminently, radiologists Stone, Earl Miller, and Bertram Low-Beer--also formed close ties with the Radiation Laboratory. (During the war, Miller would serve as liaison between the two groups.) This mutually advantageous arrangement allowed UC physicians in San Francisco to use radioisotopes from the cyclotrons at the "Rad Lab" and gave biomedical researchers at Berkeley access to human subjects for clinical trials at UCSF. Hamilton, for example, in addition to teaching courses at UCSF, was responsible for the operation of Berkeley's 60-inch "medical cyclotron," which produced the majority of radioisotopes used in biomedical research at the university.

In 1939, Hamilton and a UCSF internist, Dr. Mayo Soley, reported on thyroid uptake studies in patients using radioiodine. Later that year, Hamilton and Soley became the first to use radioiodine in the treatment of hyperthyroidism. The University of California would continue to be a leading center of research into the treatment of this disease.

THE WAR YEARS, 1942-1945

The U.S. entry into the Second World War led rapidly to the enlistment of the University of California in the war effort. Portions of Berkeley's Crocker Lab, previously used for experimental out-patient treatment with radioisotopes, were commandeered by the Army and the Rad Lab, which built a perimeter fence around the facility and declared it off-limits for the duration of the war.

In early 1942, John Lawrence's work on radiophosphorus was moved from Crocker to the newly completed Donner Laboratory, another privately funded research center on the Berkeley campus, leaving Hamilton as director of Crocker and its 60-inch cyclotron. Patients treated at Donner were referred to John Lawrence by physicians and hospitals in the Bay Area. Like the prewar Crocker Lab, the Donner Lab became, in effect, a biomedical adjunct to the Radiation Laboratory. Increasingly, however, the conversion of the campus to military-related research interrupted this work.[5]

The variety and extent of human radiation experiments in the early work of the Donner and Crocker labs remain unknown, but recently discovered documents may shed light upon the informal nature of referral and consent procedures followed in such cases.

In September 1941, the acting manager of the Veterans Administration (VA) hospital in San Francisco wrote to John Lawrence, denying permission for Hamilton to inject a patient there with radiophosphorus, following a discussion between Hamilton and a visiting medical inspector from the VA

Central Office in Washington, D.C. The VA's letter to Lawrence gives the following reason for this refusal:

> There has been no formal request on the part of [the patient] or his family to continue to receive the radioactive phosphorus which we understand was administered under your direction while [the patient] was a private patient at [Berkeley's] Alta Bates Hospital
> . . . If such a request is made by [the patient] or his family this will be forwarded to our Central Office with as full an explanation of the facts as we were able to obtain from Dr. Hamilton, for the purpose of securing permission to continue this type of treatment. It is our desire to be cooperative at all times with other medical agencies where there is no conflict with our regulations."[6]

In February 1943, the U.S. Army's Manhattan Engineer District (MED) secretly contracted with UC to administer the Los Alamos Laboratory, where the first atomic bomb was to be built. The Army-UC agreement dealing with Los Alamos was designated Contract 36. The following April, Berkeley's Radiation Laboratory was similarly enlisted in the nation's service when another secret agreement, Contract 48, was signed between the Army and UC. One component of this contract, 48A, covered war-related biomedical research by Hamilton, which had actually begun the previous year with support from the federal Office of Scientific Research and Development.[7] Hamilton's war-related research under 48A involved exposing rats to plutonium and other fission products in an effort to determine the metabolic fate of such materials and hence the risk to workers at the atomic plants.

In a February 1943 letter to Stone, Hamilton described 48A research as having "the primary purpose of protection of the civilian and military population, and the protection of those individuals who may be exposed either directly or indirectly to hazards arising from the operation of the pile [reactor]. A necessary corollary to the above is the investigation of procedures for decontamination of individuals infected by fission products."[8] Throughout the war, Hamilton submitted classified monthly progress reports on Contract 48A to the Army through the MED's Berkeley Area Engineer. Ernest Lawrence was probably the highest university official to receive these reports and to know in detail of the biomedical work being done for the government.

In August 1942, radiologist Robert Stone became director of the Health Division of the University of Chicago's Metallurgical Laboratory, which was also under government contract to investigate the biomedical hazards faced by those working on the atomic bomb. In that role, Stone oversaw Hamilton's work with radioisotopes at Berkeley and also took part in a related Army-funded wartime project, which followed the cases of terminal cancer patients receiving high doses of whole-body x rays for treatment at hospitals in San Francisco, Chicago, and New York. The purpose of the latter project was to determine the effects of external radiation on atomic industry workers.[9] In another Army-supported project concerned with radiation, Stone, starting in 1942, used MED funding to track the effect of internal and external radiation upon the blood of arthritis patients receiving either radiophosphorus or whole-body x rays as part of their therapy at University Hospital in San Francisco. In 1943, this part of the project was given the designation Contract 48C.[10]

In John Lawrence's war-related work, military personnel inhaled trace quantities of radioactive

isotopes of the noble gases and nitrogen in a study of the causes and cure of decompression sickness.[11] For this project, begun under the wartime Office of Scientific Research and Development, Lawrence relied upon volunteers from the campus Reserve Officers Training Program.[12]

During spring 1943, at the request of Robert Oppenheimer, the scientific director at Los Alamos, Hamilton and Stone also investigated the possibility of using radiological agents to poison enemy troops.[13] Polonium, strontium, tantalum, plutonium, protoactinium, and zirconium-niobium were among the agents eventually considered. In a "Review of Possible Applications of Fission Products in Offensive Warfare," sent to the Army in May 1943, Hamilton reported that the most promising method of radiological warfare would involve internal infection of the lungs and digestive tract by fission products.[14] Inhalation was determined to be the most effective method for deliberately introducing fission products into the body. Two months earlier, in a letter to Stone, Hamilton had described a newly developed technique in which short- and long-lived fission products "can be suspended in the air and their distribution in the body determined following inhalation of these substances." In the letter, Hamilton envisioned carrying out experiments using fission products on human subjects: "In addition it is planned to evaluate both the distribution and radiation effects of the raw fission mixture containing the long life material upon human leukemia patients."[15]

For Hamilton, radiological warfare became a continuing interest, extending well after the war. However, with the possible exception of a single experiment in fall 1945--involving a volunteer in Hamilton's lab, who inhaled a short-lived isotope of zirconium--no evidence of human experiments associated with radiological warfare by either Hamilton or Stone has yet come to light.[16]

In mid-1944, following the recognition of plutonium's toxicity, that element became the focus of renewed interest to Hamilton and the Army. Because it was now recognized that animal studies could not be accurately scaled to man in the case of plutonium, plans were drawn up at Berkeley and other MED-contract facilities to expand the Plutonium Project to include research on human subjects. In January 1945, Hamilton informed the Army that "[i]t is planned here at Berkeley to undertake, on a limited scale, a series of metabolic studies with [plutonium] using human subjects."[17]

The first injection of a human subject with plutonium under Contract 48A occurred at University Hospital in San Francisco on May 14, 1945. The subject, Albert Stevens, designated CAL-1, was a 58-year-old male believed to have stomach cancer. A biopsy conducted shortly after the injection, however, revealed a gastric ulcer instead of the suspected cancer. Stevens was injected with approximately 0.932 micrograms of a mixture of plutonium 238 and plutonium 239 in a solution.[18]

In late summer 1945, Hamilton informed the Army that "the next human subject that is available is to be given, along with the Pu238, small quantities of radio-Yttrium, radio-Strontium and radio-Cerium." The purpose of the experiment, Hamilton wrote, was to "compare in man the behavior of these three representative long-lived Fission Products with their metabolic properties in the rat, and second, a comparison can be made of the difference in their behavior from that of Plutonium."[19] This study was to take place beginning sometime in the following two months. However, no evidence has been found of another plutonium injection at UCSF during this time.

Supplemental Volume 1

EARLY POSTWAR RESEARCH, 1946-1947

By the end of the war, the biomedical program at Berkeley was proceeding on two parallel tracks. As is evident from Hamilton's postwar progress reports to the Army, the joint Berkeley-UCSF group planned to continue its metabolic studies of various fission products, including experiments on human subjects, pending the continuation of Army support and funding under Contract 48A. In late August 1946, for example, Hamilton informed the Army that "[t]he metabolism of radium, actinium, uranium, americium and curium will be studied in animals, and whenever possible in human subjects." The metabolism of thorium, protoactinium, and neptunium had already been studied in animals at Berkeley, Hamilton reported, "but it is planned if possible, to investigate the behavior of these three fissionable elements with human subjects."[20] In his August 1946 report to the Army, Hamilton had explicitly pointed out how the link between Berkeley and UCSF facilitated human subject research:

> It should be added that studies in the human, using both fissionable elements and the fission products, are made possible through the use of clinical material at the University of California Medical School at San Francisco. The fact that both Doctor John H. Lawrence and the writer are members of the staff of the medical school greatly facilitates any human studies which may be undertaken.[21]

In another report to the Army that fall, titled "Plans for Future Biological Research," Hamilton, possibly with an eye to securing postwar funding, once again emphasized the inherently dual nature of his research:

> There are military considerations which can be significantly aided by the results of properly planned tracer research. The distribution of Fission Products and the production of induced radioactivities by an atomic explosion, as well as the possible military application of radioactive warfare with either the long-lived Fission Products or induced radioactivities, such as radio-Tantalum, may deserve evaluation in the future. A great deal of the information already acquired by tracer techniques and the future effort outlined in this report, is directly applicable to answering some of these problems should they arise.[22]

While Hamilton planned to continue the tracer metabolism studies he had begun under Contract 48A, Stone--who had meanwhile returned to UCSF from Chicago--proposed resuming and expanding the clinical radioisotope and teletherapy research that had been curtailed because of the war, with support from the Army's Contract 48C. Working with other UCSF colleagues already affiliated with Berkeley's Rad Lab--including radiologists Miller and Low-Beer--Stone intended, specifically, to further the pioneering prewar work with radioiodine. John Lawrence had a similar interest in pursuing research on radiophosphorus.

In order to coordinate this postwar research, John Lawrence proposed that a separate Division of Medical Physics (DMP) be created under his direction. Although nominally a part of the Berkeley

Physics Department, like the "Rad Lab" itself, in reality the Division of Medical Physics was essentially autonomous, and its activities were centered upon the Donner Laboratory. The "primary purpose" of that laboratory, wrote Lawrence after the war, was "clinical investigation of some of the diseases which are not now well understood or successfully treated."[23]

Like Hamilton and Lawrence, the other members of the fledgling DMP also held joint appointments in the Radiation Lab and at the UC Medical School in San Francisco. At the insistence of the Medical School, however, the arrangement approved by Sproul specified that "all studies related to human beings should be under the control of [physicians] on the San Francisco campus responsible administratively to the Dean of the Medical School."[24]

As documents from the university's archives make clear, relations between the DMP and UCSF were severely strained from the start. Part of this strain derived from the historical fact that the Medical School in San Francisco and the academic biomedical departments on the Berkeley campus were in perpetual competition over matters of resources, oversight, and status. This competition, a consequence of the splitting of responsibility for the training of doctors between the main campus and the Medical School in the aftermath of the 1906 San Francisco earthquake, was exacerbated by the efforts of Ernest and John Lawrence to persuade the university's president to move the Medical School to the Berkeley campus.[25]

However, another more substantive point of contention between the DMP and the Medical School was the question of human experimentation. Although he had signed the agreement creating the DMP, John Lawrence admitted to being "seriously concerned" over the limitation imposed upon human experimentation at Berkeley. He pointedly appended his own statement to the charter, proclaiming that "there should be no limitation or ham-stringing of the freedom of the members of the subdivision of medical physics and others in the Medical School to carry on treatment or investigations in Berkeley if research were the prime interest."[26]

As a result of this unresolved dispute, oversight of DMP activities by the Medical School and its dean, Dr. Francis Smyth, appears to have been minimal at best. In practice, the deliberately ambiguous nature of the DMP-UCSF agreement, and the still-classified nature of the research being carried out under Army contract at Berkeley, meant that the Division and its handful of affiliated UCSF physicians were able to operate with virtual autonomy.[27] An illustration of how members of the DMP doing classified research had to be careful about sharing information with their erstwhile UCSF collaborators is evident in Hamilton's response to a February 1945 letter from Stone, who had suggested that their prewar colleague, Mayo Soley, be enlisted in secret Army-funded radioiodine studies using human subjects. Hamilton proposed, instead, that the experiments be conducted "with some of the people" at Berkeley, and warned that Soley "is an individual of more than average ability and . . . would soon realize that something very peculiar was going on."[28]

Despite Hamilton's previously announced plans to carry out several human radiation experiments using plutonium and other fission products, only one such additional case prior to 1947 has been found. In April 1946, CAL-2, Simeon Shaw, a four-year-old Australian boy with bone cancer, was injected with a mixture of plutonium 239, cerium, and yttrium.[29] The fact that this injection closely fits the profile of the experiment proposed by Hamilton the previous September in his report to the Army strongly suggests that CAL-2 was part of the research conducted under the auspices of the Plutonium Project. According to his August 1945 report to the Army, Hamilton's interest in cerium and yttrium stemmed from Berkeley's search for a material useful in removing plutonium from bone.[30]

However, other aspects of this case--including the fact that the subject was a child, the use of several different radioelements, and the lack of follow-up investigations--do not follow the pattern of previous MED-funded plutonium injections, and suggest that another purpose of this experiment might simply have been to gain knowledge about how and where radioelements would localize in the body. While such knowledge might be of subsequent medical value in devising treatment, it was of no therapeutic worth to this individual patient. Thus, CAL-2 would seem to have been a multi-purpose experiment; the intent being to gain knowledge of medical and military value.[31]

The documents in the CAL-2 case contain no explanation for the seven-month delay between Hamilton's proposal for injecting a human subject with a combination of plutonium and other radioelements, and the time the experiment was actually carried out. Nor is there definitive evidence concerning the selection of this particular subject, who was referred to UCSF by specialists in Sydney, Australia, following a diagnosis of osteogenic sarcoma. Indeed, CAL-2's medical file contains no reference to the radioisotope injection, with the exception of a two-page discharge notice, dated June 11, 1946, and titled "To Whom It May Concern." Written by the patient's UCSF surgeon, it noted that during CAL-2's hospitalization:

> Generous sections of the [tumorous] bone were taken for biopsy as well [as] studies to determine the rate of uptake of radio-active materials which had been injected prior to the surgery, in comparison with normal tissues. At the time of writing, these data are not available in the chart and can be obtained by responsible individuals by writing to Doctor Earl Miller of the Department of Roentgenology in the University of California Hospital, San Francisco, 22, California.[32]

In late December 1946, following a renewed request to the Army by Hamilton for additional plutonium "to be used for certain human studies," and a further progress report on CAL-1, the Army ordered a halt to research upon human subjects by the Berkeley-UCSF group.[33] The following week, the civilian AEC took over responsibility for all nuclear research, including Contracts 36 and 48 with UC, and reaffirmed the Army's temporary suspension of human experimentation at UCSF.[34]

In March 1947, at the urging of the former director of the Army's Medical Section and architect of the Plutonium Project, Col. Stafford Warren, the AEC approved the resumption of isotopes shipments and human subject research by former MED contractors, including the University of California.[35] As before, however, documents that specifically referred to human experiments "and might have adverse effect on public opinion or result in legal suits" were to remain classified.[36] Originally classified "Restricted," these documents were later downgraded to "Official Use Only." They have now been entirely declassified.

Also as part of the new AEC policy, the University of California, as a former MED contractor, was allowed a broad use license for the medical application of radioisotopes. Under this arrangement, the university was exempted from the AEC requirement that individual researchers proposing to use radioisotopes on human subjects gain approval from an AEC-appointed board of reviewers. Instead, under AEC rules, such applications were to be reviewed by a committee established within the university. (See chapters 1 and 6 in the Advisory Committee's final report for a discussion of the evolution of rules governing isotope distribution.) Despite a recommendation from the AEC legal counsel that any human

subjects involved in commission-sponsored "clinical testing" sign a written release, AEC General Manager Carroll Wilson in April 1947 ultimately bowed to pressure from Stafford Warren and the other members of the AEC-appointed Interim Medical Advisory Board, who urged that the consent procedure consist instead of written certification by at least two attending physicians as to "the patient's understanding state of mind, to the explanation furnished him, and to his willingness to accept the treatment." Such clinical testing was to be "in the course of treatment of patients," Wilson advised, and "treatment (which may involve clinical testing) will be administered to a patient only when there is expectation that it may have therapeutic effect." Finally, "the decision as to the advisability of the treatment will be made by the doctor concerned."[37] (See chapter 1 of the Committee's final report.)

In another concession to AEC's contractors, Wilson also assented to the recommendation of Warren's Interim Medical Advisory Board that up to 20 percent of the time of a contract could be devoted "to pursuing lines of research which appear fruitful to [contract researchers], even though not immediately related to specific items in the approved program for the particular project." This clause, which was later amended to 15 percent of the time of the contract, would presumably have allowed the kind of experiments aimed at answering questions of medical as well as military worth already known to be of interest to UC researchers.

By the summer of 1947, government-supported research involving human subjects had resumed at UC under Contract 48A. That June, a teenage bone cancer patient at Chinese Hospital in San Francisco, CAL-A, was injected with approximately 0.25 microcuries of americium at UCSF. Although most patient records for CAL-A were evidently destroyed, a handwritten notation in the surviving portion of the patient's file by one of Hamilton's assistants specifies that "we will use same procedure as with Mr. S," a possible reference to CAL-1, Albert Stevens. "See JGH [Hamilton] for particulars."[38]

In July 1947, a third human subject at UCSF, Elmer Allen, CAL-3, received an injection of 0.006 micrograms of plutonium 238 in his left leg before that leg was amputated.[39] In the case of CAL-3, a UCSF physician associated with the Berkeley group, Dr. Low-Beer, was one of two doctors who attested in writing to the patient's understanding and consent to the procedure, as required by the AEC's April 1947 regulation. Because records for CAL-A are incomplete and the records of a later case, CAL-Z, remain undiscovered, it is unclear whether the policy was followed in these cases.

The CAL-3 experiment seems to have been a case of what the AEC now defined as "clinical testing"--i.e., while the procedure was not intended to be of therapeutic value to the patient, it was expected to yield information of medical usefulness in understanding the behavior of radioelements in the body, and ultimately even in devising future therapies. Since the radioelement in this case was plutonium, the experiment was also of potential military interest.

The fact that the documentation provision of the AEC's newly devised consent procedure was followed in this single case seems indirect evidence that the CAL-3 experiment was considered, by the researchers themselves, to be part of the clinical testing program outlined by the commission. No written proof of consent was required, or sought, in either of the first two plutonium injections at UCSF.

However, as discussed in more detail in chapter 5 of the final report, the AEC requirements also precluded experimentation that was not of potential benefit to the patient. While the CAL-3 research may have been directed at providing data useful to understanding and treating cancer as well as to the military, there is no evidence that it was designed to benefit the patient at the time, which would have been a violation of the AEC guidelines.

Although subsequent oral history accounts of the UC plutonium injections remain sketchy and

sometimes contradictory, one document may shed light on the question of consent in the cases prior to CAL-3. This document, a memorandum dated December 30, 1946, from an Army representative at Oak Ridge to the MED Area Engineer at Berkeley, notes that "preparations were being made for injection in humans by Drs. Stone and Miller . . . These doctors state that the injections would probably be made without the knowledge of the patient and that the physicians assumed full responsibility. Such injections were not divergent from the normal experimental method in the hospital and the patient signed no release. A release was held to be invalid."[40] Unfortunately, there is no explanation in this or any subsequent document as to why a release would have been deemed invalid. However, as noted in chapter 5 of the Committee's final report, studies conducted without a release were common at the time.

Apart from the plutonium and americium injections done under Contract 48A, most of the postwar work with radioisotopes that was carried out by the DMP-UCSF group was not classified, and evidently concerned the administration of radiophosphorus and radioiodine for therapeutic purposes. While still perhaps considered technically experimental by many physicians, these procedures were nonetheless becoming increasingly routine. Hamilton's records, for example, indicate that between 1938 and April 1946 some 570 patients suffering from leukemia, lymphosarcoma, or polycythemia vera were treated with radiophosphorus at UCSF or Berkeley.[41] Similarly, a 1950 report by Earl Miller on the use of iodine 131 at the University of California records that 114 UCSF patients with hyperthyroidism were treated with iodine 131 between September 1945 and November 1949.[42] There can also be little doubt that the principal purpose of these treatments was therapy for the patient.

Elsewhere, however, the line between clinical treatment and what the AEC permitted under "clinical testing" seems to have remained indistinct in at least some cases--as even the researchers themselves occasionally acknowledged. For example, the fact that the results of the radioiodine studies were also of military interest to the agency funding the research (AEC) was pointed out by Hamilton in an undated proposal for expanding human radioiodine studies under Contract 48C in 1947-1948:

> Radioiodine is one of the fission products freed in the atmosphere in regions adjacent to piles. It is also set free with great activity at the time of bomb explosions. It therefore is important to study its effects on humans. Opportunity for such study is found in the course of treatment of hospital patients for thyroid disturbances of either benign or malignant character.[43]

As Hamilton went on to note in this proposal, the research being carried by the DMP-UCSF group was by its nature dual-purpose, in that the information gained was of clinical as well as military interest:

> Other aspects of importance in the 48C program are the observation of the effects of total body radiation from external and internal sources. In this work, advantage is taken of the availability of human subjects who are under treatment with x-rays to the entire body, or with radio-active phosphorus or some other radio-active isotope. These studies are made in the course of treatment administered for the patient's condition.[44]

Miller likewise acknowledged the implicit connection between clinical treatment and broader research in an April 1947 request to Oak Ridge for iodine 131, which was to be used as part of 48C's program to determine the uptake, distribution, and excretion of that isotope: "Patients with diseases are

used in order that high doses may be administered," Miller wrote. "The fact that they have disease is incidental and the medical aspects of these patients are cared for outside the project." Miller made the same argument the following year, when he renewed his request for radioiodine: "The fact that these patients have carcinoma of the thyroid makes the administration of such large doses permissible."[45] In such cases, clinical testing seems to have been carried out independent of any regard for therapeutic benefit.

It appears that only belatedly--in March 1949--did the AEC Subcommittee on Human Applications formally create a mechanism by which such cases of clinical testing could be reviewed and approved. Acknowledging "that there may be instances in which the disease from which a patient is suffering permits the administration of larger doses for investigative purposes," the AEC declared that approval would be granted only if the treatment was deemed unlikely to cause harm, the patient consented, and full responsibility for the work was assumed by "a special committee of at least three competent physicians in the institution in which the work is done."[46]

POSTWAR RESEARCH MATURES, 1948-1950

The fact that Stone, Hamilton, and others at Berkeley remained deeply involved in other classified work for the government further blurred the distinction between their clinical and military-related research. By spring 1948, Hamilton, in addition to his work for the AEC, was an adviser to the Army Chemical Corps on radiological warfare and a consultant to Fairchild Aircraft on the Nuclear Energy Propulsion for Aircraft (NEPA) program, an Air Force-funded project to design a nuclear-powered bomber.[47] During this same time, Stone was also a consultant on NEPA and had become a partisan in a secret government debate over the nuclear airplane, urging that volunteers be used in experiments involving high doses of whole-body irradiation.[48]

Although plutonium injections at UCSF evidently ended with CAL-3 in July 1947, Hamilton's tracer research on human subjects continued at least into 1948. That March, for example, Hamilton, reporting to the AEC on his plans for Contract 48A during 1948-1949, wrote the commission's area manager: "Under appropriate and suitable circumstances, it is highly desirable to conduct human tracer studies with certain fission products and fissionable elements . . . [f]irst to establish the metabolic behavior of these substances in man . . . [s]econd, to investigate the potential diagnostic and therapeutic applications. . . . The human studies of this character will be undertaken with Dr. R. S. Stone at the University of California Medical School."[49]

Additional evidence suggests, however, that the purpose of this research was now increasingly concerned with identifying radioisotopes that might prove efficacious in the treatment of diseases like cancer. In this connection, one of Hamilton's former colleagues, Patricia Durbin, observed in an Advisory Committee oral history interview that the bulk of the postwar radioisotope work by the DMP-UCSF group was part of a wider search in nuclear medicine for radioactive "magic bullets"--isotopes that would cure different cancers selectively by localizing in different parts of the body. One such "bullet" had already been discovered at Berkeley--iodine 131, which localizes in the thyroid.[50]

Although the search for radioelement magic bullets can be traced to the dawn of nuclear medicine in the mid-1930s, the discovery of nuclear fission gave the hunt added momentum. In May 1946, Hamilton and Stone, reporting to the Army on promising future areas of biomedical radiation research, succinctly described the "magic bullet" thesis:

> The fundamental fact has already [sic] demonstrated that if a sufficient quantity of a radioactive material can be made to localize in a diseased structure of the body such as the thyroid gland, intense irradiation of that organ will take place without damage to adjoining normal tissues. The widespread availability of adequate quantities of the artificial radio-elements will make possible a more rapid and effective search for radioactive compounds which may be localized in malignant tissues. . .[51]

Two months later, Hamilton wrote to a physician colleague that "[t]o date no fission products, aside from radioactive iodine, have been employed for any therapeutic purposes." He nevertheless held out hope that such a magic bullet might be found: "There is a possibility that one or more of the long list of radioactive elements produced by uranium fission may be of practical therapeutic value." The following year, in the draft of a paper on the medical application of radioactive tracers, Hamilton identified strontium, zirconium, and yttrium alongside phosphorus and iodine as prospective magic bullets.[52]

The search for radioisotope magic bullets at UC was doubtless given additional impetus--as well as funding--by a state-wide "Cancer Project" established in 1947. This project drew upon more than a million dollars in public and private bequests for research aimed at eradicating cancer, and it produced annual reports on this research for at least the next seven years. Starting in 1948, the state's Cancer Project became a major source of funding for the research being conducted by Hamilton and Stone, as well as by members of the Berkeley's Division of Medical Physics.[53]

Evidence from the UC archives indicates that, by 1948-1949, the focus of such magic bullet search was centered upon two radioisotopes--zirconium 95 and columbium 95 [the modern term for columbium is niobium]. Subsequent human subject research carried out at UCSF with these two isotopes seems to indicate, however, that even in such cases, clinical testing often remained multi-purpose.

In January 1948, for example, the Radiation Laboratory administered a "test dose" of zirconium 95 to a 55-year-old female cancer patient at UCSF.[54] (The records of the patient, CAL-Z, could not be located, so there is no evidence on the consent procedure followed in this case.) The following August, the report of this injection was denied declassification by the AEC, "since it specifically involves experimental human therapeutics."[55] Although proscribed from appearing in the open medical literature, the classified Rad Lab report on CAL-Z was forwarded to a variety of defense-related organizations, including the Air Force headquarters of the NEPA project.

A progress report on Contract 48A activities for 1948-1949 notes that "[r]adiozirconium and radiocolumbium, after considerable experimentation, was prepared in a form usable without any untoward effects to humans." The report goes on to record the effects upon a total of seven patients injected with columbium or zirconium, or some combination of the two: "Selective concentration of Zr95 and Cb95 was found in two patients with malignant melanoma, in one patient with metastatic carcinoma from the large intestine, and one patient with breast tumor. In three other patients with breast tumor no selective uptake was found in the tumor tissue."[56] A handwritten notation in a Hamilton file marked "Human Studies" suggests that one of these subjects may have been a 30-day-old infant, injected with radiocolumbium three days before her death in December 1948. Neither medical records nor a death certificate for this patient could be located in UCSF archives or among state records, however.[57]

Subsequent documentation reveals that medical interest in zirconium and columbium continued

well after the war at Berkeley and UCSF. A 1950 grant renewal application to the state cancer program by Drs. Stone and Low-Beer noted that "[s]elective localization of Zr95 and Cb95 have been done on 11 patients, but the results have not been analyzed." The application made explicit the connection with magic bullet research: "The search for materials that will localize in a tumor will give us a diagnostic tool, and if the developmental localization is sufficiently great it will provide a therapeutic tool."[58]

Stone, for his part, also continued to direct the program of clinical testing with radioiodine that had resumed after the war under Contract 48C. Here again, these experiments seem to have been of both medical and potential military interest. In an April 1950 report titled "Biological Effects of Radiations from External and Internal Sources," Stone recounted the results of a recent investigation involving mental patients at San Francisco's Langley-Porter Clinic, 65 of whom were given iodine 131 in an effort to determine whether any abnormal thyroid function existed in patients with mental disorders. Since no abnormal thyroid function was found, these patients were deemed a normal control group. Subsequently reporting on this experiment in an unclassified meeting on the NEPA project, the director of the Langley-Porter Clinic cited the consent procedure used in this case--the patients had evidently been asked if they objected to the injection of the radioisotope--as evidence that there might be less concern with radiation among human subjects than many researchers feared.[59]

EXPANSION AND CONTROVERSY, 1948-1952

In November 1948, the University of California signed another agreement with the AEC, Contract 10, which provide support for "non-programmatic" research connected with atomic energy, including biomedical work previously done under the auspices of Contract 48 and the Radiation Laboratory.[60] The evident intent of Contract 10 was to free UCSF researchers from having to submit research proposals to the AEC through the Rad Lab. Starting in June 1949, Project 2 of the contract--"research on the physiological effects of radiation," under the direction of Stone--provided support for extending the earlier 48C studies using teletherapy and radioisotopes begun by Stone, Miller, and Low-Beer. An additional part of the program was concerned with identifying the causes and cure of radiation sickness.[61]

With the postwar growth of research in nuclear medicine, the still-unresolved conflict between the Medical School at UCSF and Berkeley's Division of Medical Physics (DMP) over human experimentation once again came to the fore. As early as November 1946, John Lawrence had proposed using private funding to establish a Metabolic Unit, for in-patient treatment and clinical testing involving radioisotopes, at Cowell Hospital on the Berkeley campus. This unit would have expanded and made routine the out-patient clinical research using radioisotopes begun before the war at Crocker and Donner laboratories. However, since the creation of this unit would violate the earlier agreement prohibiting human subject research on the Berkeley campus, the proposal was blocked by the Medical School and Dean Smyth.

Undeterred by this rejection, and prompted by the possibility of obtaining AEC funding for the new Metabolic Unit, Lawrence again raised the issue with President Sproul two years later.[62] The renewal of the Berkeley-UCSF feud sheds light not only on the controversy over human experimentation at the university, but also on the considerable impact of AEC funding. In a February 1949 letter, Dean Smyth complained to University President Robert Sproul that relations between the Medical School and the Division of Medical Physics had become "untenable. . . . There is lack of contact and no consultation

with varied clinicians. We have no knowledge of what is being done."[63] In a confidential meeting with Smyth two days later, Sproul, according to notes of the conversation, acknowledged to Smyth that he shared "some of his misgivings, but . . . described to him the two pressures which are now upon me, namely, (1) a report of a committee representing both the Medical School and Medical Physics, recommending that I approve the establishment of the Metabolic Unit, and (2) the imminent meeting of an AEC Committee from which Dr. John Lawrence can get funds for his work, if I inform him that the Clinic has been approved."[64]

Still formally enjoined from conducting research using human subjects on the Berkeley campus, Lawrence carried out a series of blood volume experiments using trace amounts of radioiron and prisoner volunteers at San Quentin in March 1949.[65] Prisoners were used so that long-term baseline data on normal subjects could be gathered. Ten prisoners were involved, and written consent from the prison's warden and state correction officials was obtained prior to the experiments being carried out. According to Lawrence's own later account, only verbal consent was obtained from the prisoners themselves, although they received written acknowledgment of their contribution. A university official raised concerns about the possible legal consequences of these experiments the following August, after local press accounts appeared, but those concerns were evidently allayed, since Lawrence carried out a second series of radioiron experiments at the prison in 1951.[66]

Although the prohibition against human subject research on the Berkeley campus remained in effect, there was apparently no restriction upon the affiliation that Lawrence and his DMP colleagues enjoyed with metabolic wards and isotope units conducting clinical research at other medical facilities around the Bay Area.[67] Between 1947 and 1952, using funding from the AEC, the National Cancer Institute, the California Cancer Project, and private sources, physicians jointly affiliated with the DMP and UCSF carried out clinical research at the Laboratory for Experimental Oncology of San Francisco's Laguna-Honda Home, Highland-Alameda Hospital in Oakland, Ft. Miley Veterans Hospital in San Francisco, and the Langley-Porter Clinic in San Francisco.

Most of these studies evidently involved radioiodine and radiophosphorus, but tritium, radiogold, and carbon 14 were also used in research trials. Evidence suggests that both patients and paid healthy subjects were used in this research. In cases where the subjects were paid volunteers, no signed consent was required, according to a 1952 letter from John Lawrence.[68] As had been the case before the war, patients were evidently referred to DMP researchers by physicians at nearby hospitals. In an April 1953 document, Lawrence estimated that three-quarters of the patients being treated at Donner were referred from Highland and various VA hospitals in the area. "We don't take patients here who have a problem for which there are standard treatments," he explained in this report.[69]

The creation of an Isotope Unit at Laguna-Honda's Laboratory of Experimental Oncology (LEO) was another tangible result of the collaboration between members of the DMP-UCSF group--specifically, John Lawrence, Hardin Jones, Miller, and Low-Beer--and the director of a medical facility in the Bay Area.[70] Patients were evidently referred to the LEO by the Tumor Board at UCSF, whose chairman at the time was Robert Stone.[71] Although supported by state, National Cancer Institute, and private funds, the research and "data gained [at the LEO] upon the fate of test doses of various fission products in man, is of interest to the Atomic Energy Commission," pointed out one Berkeley researcher in a 1949 letter to the Commission's Division of Biology and Medicine.[72]

Oversight and patient consent procedures in these collaborations apparently depended upon the rules of the particular institution where the research occurred. In 1951, a controversy arose over certain

medical procedures (not involving radiation) and the consent form employed at Laguna-Honda and the LEO. As a result, in October of that year a symposium was held at UCSF on the ethics of human experimentation. Due in part to this controversy, but also to budget cuts and reorganizations, the LEO was shut down in 1953.[73]

Throughout this period, suspicions persisted among the top leadership of UCSF that human subject research was being carried out at Donner Lab on the Berkeley campus. During May 1951, in appointing a second review committee to resolve the ongoing feud between the Medical School and the DMP, President Sproul noted that "there is still apprehension in the Medical School with reference to the safety of patients under study in Berkeley, that clinical studies, it is stated, have been undertaken in the Division of Medical Physics without consultation with the Division of Medicine."[74]

Indeed, there is anecdotal evidence that John Lawrence and his colleagues in the Division of Medical Physics were able to circumvent oversight by exploiting unclear lines of authority and invoking their AEC connection. This evidence comes from a 1979 interview with Cornelius Tobias, a close colleague of Lawrence and a founding member of the DMP:

> I don't recall any instance where we as part of our medical physics professorial duty would treat patients. We treated very obviously under financial support and agreement from the Atomic Energy Commission. And of course the Medical School was very unhappy about that, or certain individuals in the Medical School. I might say this, that when you say, 'whole Medical School,' that's not correct, because Lawrence had friends, very good friends, in the Medical School, who felt that it was very logical for him to proceed as he did . . . And once they began to criticize it--I know because later it came up--then the standard answer was that this is part of the Radiation Laboratory activities and financed by that. John Lawrence is associate director of the Radiation Laboratory [and the] medical agreements and protocols have been arranged with the Washington office of that agency.[75]

In March 1952, the six-year-long battle with the Medical School ended in John Lawrence's favor when an in-patient radioisotope treatment facility, the Donner Pavilion, was officially opened at Cowell Hospital.[76] The purpose of the Donner Pavilion, Lawrence wrote the AEC the following November, was "to provide hospitalization . . . for patients so that we can carry out studies on them in connection with our work at Donner Lab," and also to provide bed space in the event of nuclear war or a peacetime atomic accident.[77]

Donner Pavilion was, in fact, just one part of a burgeoning complex of nuclear medicine facilities established by the University at this time. In 1950, with support from the AEC, Stone had dedicated a Radiological Laboratory on the UCSF campus to house a 70-million electron volt "Synchrotron," ultimately to be used in teletherapy. In 1951, again with AEC support, Stone also opened a Radioactivity Research Center on the medical campus.[78]

The human subject research conducted by Stone, Hamilton, and their colleagues in the Division of Medical Physics was, by this time, the subject of controversy well beyond the confines of the Berkeley campus or even the state of California. Indeed, some of the most vocal criticism came from within the

AEC itself. Following an April 1948 visit to the Berkeley campus, the chairman of the AEC's Advisory Committee for Biology and Medicine, Dr. Alan Gregg, criticized Stone's x-ray treatment of arthritis patients as "not justified."[79] Stone's defense--that the choice of patients and treatment had been by UCSF doctors, not the AEC--was dismissed as irrelevant by Gregg, who wrote that he and his colleagues "do not wish to collaborate in clinical investigations with physicians in whose considered judgment they do not have confidence."

Another strong critic of human radiation experiments was the director of the AEC's Division of Biology and Medicine, Dr. Shields Warren. "Don't like 300 r [rad or roentgens] or so for arthritic patients," Warren wrote in his personal journal following an April 1948 meeting with Stone. The following day, Warren continued on this theme in his discussions with Stone: "Much condemnation of use of pts [patients]."[80] A few months later, it was Warren who reaffirmed the decision of a lower AEC official not to declassify the Rad Lab's report on the zirconium injection, CAL-Z, despite an appeal from Berkeley. That report had been denied declassification in part, wrote the AEC official, because "it appears almost impossible to rewrite it in an acceptable manner, which would not jeopardize our public relations."[81]

In July 1949, responding to Stone's position on the NEPA debate, Warren advised the UCSF radiologist that he was "taking an increasingly dim view" of human experiments. "Consequently, record me as voting against human experimentation," Warren wrote.[82] The previous January, Warren had rejected a request from John Lawrence to label a drug with radioactive carbon 14 in order to better trace its course in patients.[83] Warren's objection was made on the grounds that C-14's use in humans had not yet been proven safe. Lawrence, however, appealed this rejection to the AEC's Subcommittee on Human Applications at Oak Ridge, and was subsequently granted permission to use the isotope.[84]

In August 1949, in what appears to have been an effort to close a possible loophole in the AEC's control of isotopes, Warren wrote to John Lawrence that isotopes were to be used on human subjects only after review and approval by the Subcommittee on Human Applications of the Committee on Isotope Distribution, even if the isotopes had been produced in the laboratory where they were to be used. "Since this procedure has not been uniformly followed in the past," Warren chided, "we are writing to acquaint you with the appropriate details."[85]

Hamilton appears to have been aware of Warren's misgivings as well. In November 1950, when he was unable to attend a Washington conference on a soldier's ability to fight after being exposed to radiation, Hamilton wrote to Warren to share his ideas on the subject. Hamilton wrote it was "very desirable to determine in man the range of total body radiation required to induce an appreciable decrease in his capacity to execute intricate tasks for which physical well-being is essential." For that purpose, Hamilton proposed exposing animals or humans to near-lethal levels of radiation. He preferred using large monkeys to smaller animals, because of the similarities to man, and concluded that, "If this is to be done in humans, I feel that those concerned in the Atomic Energy Commission would be subject to considerable criticism, as admittedly this would have a little of the Buchenwald touch."[86] Finding healthy volunteers, he mused, also would be difficult.

CONSOLIDATION AND RETRENCHMENT, 1953-1974

By the early 1950s, the continuing search for radioisotope "magic bullets" had apparently prompted at least one new tracer experiment by the Berkeley group using human subjects.[87] In May

1954, Hamilton and two colleagues reported on the results of an experiment in which eight patients with thyroid disorders were administered radioactive astatine, which was believed similar to radioiodine in its effects.[88] The absence of follow-up studies suggests, however, that this line of research was subsequently abandoned as unfruitful.[89]

Although such experiments were no longer classified, in at least one case Hamilton used secrecy and "need to know" to sidetrack basic research and delay a potentially important scientific discovery. In a June 1954 letter to AEC official Walter Claus, classified secret, Hamilton took credit for deceiving a former student of his who had accidentally discovered that radioiodine from nuclear testing was being concentrated in beef thyroids in Tennessee, and who speculated that such testing might also account for increased radioiodine levels in humans worldwide. "Understandably," Hamilton wrote to Claus, "I saw the possible implications of what he brought to my attention and attempted to subdue his marked degree of enthusiasm by suggesting that traces of radioiodine in the Memphis area might have arisen from airborne contamination from the Oak Ridge National Laboratories."[90] "Your playing down of the matter to [the student] was certainly good judgment," Claus responded.[91]

Starting in the mid-1950s, the spectacular growth of nuclear medicine research at Berkeley and UCSF began to slow. Part of this change was undoubtedly due to the loss of two of the founding members of the DMP-UCSF group. Bertram Low-Beer died of leukemia in 1955. That same year, Hamilton was diagnosed with the leukemia that would bring about his death in February 1957. Ernest Lawrence, who had been a key supporter of the biomedical work at Berkeley, died in August 1958 of complications following surgery for colitis. In his honor, the Radiation Laboratory was renamed the Lawrence Berkeley Laboratory (LBL).

But shrinking federal funds, disillusionment with the "magic bullet" theory, and evolving technology also combined to shift the direction of research at Donner, the Radiation Lab, and UCSF away from clinical testing with radioisotopes toward medical experimentation and treatment by "big machine" teletherapy. This shift was reflected, for example, in a 1958 report by John Lawrence on AEC projects at the University of California: "We wish," Lawrence wrote, "to continue development of the new experimental and therapeutical tools of nuclear physics and chemistry and turn them to the investigation of the major unsolved problems in biology and medicine, including the radiation syndrome, cancer, hemopoietic disorders and artherosclerosis."[92]

The Synchrotron

By the time of Lawrence's 1958 report, several such investigations were already under way, and would continue well into the next decade. In November 1951, the 70-MeV Synchrotron began operation at Stone's Radiological Laboratory on the UCSF campus. Used to direct high-energy x-ray beams at deep-seated lesions, the Synchrotron was not approved for clinical application on patients until five years later. The patients chosen were believed to have less than an even chance of surviving five or more years under conventional therapies. According to a 1963 report by the Rad Lab, 388 patients suffering from advanced cancer had received treatment at the Synchrotron; 160 were still alive at the time the report was written.[93]

The programs at Berkeley and UCSF also continued to have their critics. In particular, some AEC officials charged Stone with exaggerating his claims for the Synchrotron. In a 1959 report following his visit to UCSF and the Rad Lab, for example, Paul Henshaw of the AEC Division of Biology

and Medicine questioned the efficacy of the program, while still being careful not to criticize its intent: "With respect to the Stone enterprise, it seems to me we are faced with a perpetuity situation (with prospects of meager returns at best) unless concrete steps are taken." Henshaw recommended that the AEC end its support of the Synchrotron the following year, but funding for the machine continued into the mid-1960s.[94]

While initially optimistic about the possibilities of the Synchrotron, by 1963 Stone himself concluded that, while he and his colleagues were "curing" some patients with advanced cancer, the numbers were not much better than conventional treatments. This fact was not surprising, Stone contended: because of the low survival rate of the disease, "we expected few 'cures' from the patients treated five, six, and seven years ago."[95]

Heavy Ion Therapy

During this same period, others in the Division of Medical Physics--including John Lawrence and biophysicist Cornelius Tobias--were investigating the use of heavy ion radiation on the pituitary gland to control hormone-dependent cancers. A major study of this technique had begun under Tobias in 1954, and by the late 1960s at least 250 patients, most suffering from breast cancer, were treated. Patients who received heavy ion radiation were selected on the criteria that they had not responded to conventional therapies, were under 60 years old, and were thought to have "a realistic chance of deriving benefit" from the treatment. Although early procedures using extremely high doses of radiation to the pituitary--from approximately 13,000 to 30,000 rad--were subsequently believed to have caused neurological damage in some patients, a 1967 report by a Donner Lab physician concluded that in these cases "the risk of brain damage seemed to be justified [because of the advanced nature of the disease]."[96] Heavy ion radiation was also used in the cases of six patients with brain tumors between 1962 and 1968.[97]

The Rad Lab also conducted a study on 71 patients with diabetic retinopathy, a degenerative eye disease related to diabetes. According to a report by Lawrence and Tobias, the patients used in the study were referred to Donner Lab by private physicians and received independent evaluations from two other outside physicians before being treated.[98] Moreover, by this date a consent form was routinely in use at Donner Lab.

These studies were put on hold in the early 1970s, but resumed in 1975 with pilot studies using the 184-inch synchrocyclotron and continued with the introduction of the BEVALAC in 1977. The BEVALAC used two accelerators to deliver high uniform doses of heavy ions that are used to ablate deep-seated tumors. Treatments using helium and other heavy ions continue today, although the program is constrained by recent budget cuts and the closure of the BEVALAC.

Dr. Richard Levy, a medical scientist at Lawrence Berkeley Lab who has examined patient records dating back to the late 1950s, has said these treatments were very effective given the imaging limitations of the time. In his preliminary analysis of records from the smaller studies, Levy said the majority of patients were cured of their disease, and he found no evidence of secondary malignancies or injury to adjacent brain structures. There were also no unexpected radiation-induced diseases, though more than one-third of the patients developed some delayed hypopituitary problems. However, these problems were anticipated in a significant number of cases.[99]

Radioiodine

In 1955, a follow-up study was conducted at Donner Lab of 175 patients who had received radioiodine treatment for hyperthyroidism between September 1945 and February 1952. Rad Lab documents also point to a set of experiments in the early 1960s that investigated the thyroid uptake of iodine 131 by pregnant woman and their fetuses. It is unclear from the documents available whether a formal study was carried out.[100]

Radiostrontium and the Fallout Study

In April 1954, the AEC asked Hamilton for the medical records of UCSF patients who received radiostrontium between 1942 and 1944 in experimental therapy or as a palliative for metastatic bone cancer. This request was prompted by the AEC's Project Sunshine, a then-secret program to assess the human hazards of radiostrontium from the fallout of atmospheric bomb tests. A similar concern evidently lay behind the so-called Diaper Study at Berkeley, which measured the uptake of stable calcium and radiostrontium from processed baby foods in the normal diet of infants between 1957 and 1962. The lab supplied mothers with baby food, samples of which were tested for calcium and strontium content.[101] In this study, radioelements were not introduced into the foods; rather, the Lab checked the food for "naturally occurring" content.

"Captive Population" Research

Between 1958 and 1962, John Lawrence and his colleagues at Berkeley carried out a series of experiments among so-called captive or "vulnerable" populations at San Quentin, as well as at a Napa State Hospital. One of the San Quentin experiments employed prisoner volunteers to determine the mechanism of red blood cell production. (Human studies were required because of the widely varying way that different animals metabolize iron.) A second experiment injected bone marrow from 20 paid prisoner volunteers into patients with lymphatic leukemia, who had been previously treated with radioyttrium.[102] As was the case with Lawrence's San Quentin experiments in the late 1940s and early 1950s, there is no evidence that written consent was obtained from the prisoners themselves. Prison officials permitted the study to be carried out based upon a protocol filed by Lawrence, and prisoners were compensated for their participation.[103]

Residents at the state-run mental hospital in Napa participated in an iodine 131 uptake study begun in 1958. The hospital's director described the experiments as representing "a unique opportunity for investigative work in the field of mental illness."[104] The consent procedure followed in these cases is not known.

SUMMARY

The following summary and concluding remarks concern areas of particular interest to the Advisory Committee.

Secrecy

At the University of California, as elsewhere, the invocation of secrecy for reasons of "national security" provided a convenient and effective means of avoiding further inquiry from colleagues or superiors. Even when it was not improperly used as a cloak for misdeeds, secrecy engendered suspicion--if only by an awareness of the potential for its misuse.

Significantly, however, the insistence on keeping secrets came from the government, not from university researchers, and it continued after the wartime emergency had passed. Despite the 1954 incident in which Joseph Hamilton deliberately misled a former colleague in order to guide him away from a secret project, the majority of UC researchers--Hamilton included--were eager to share the results of their classified work using human subjects with their professional peers "outside the fence."

Robert Stone, for example, repeatedly requested that the AEC declassify the data he had gathered on total-body irradiation of terminal cancer patients, so that it might be published as part of a multivolume series on wartime radiation research.[105] Stone's requests were denied declassification on the grounds that his report on the patients contained "material the release of which would be prejudicial to the best interest of the Atomic Energy Commission, in that it might result in adverse publicity and even encourage litigation."[106] Consequently, only part of the data made it into the series.

Hamilton's efforts during the same time to obtain release of his classified reports detailing the plutonium injections were similarly rebuffed by the AEC. Indeed, as late as 1949, DBM Director Shields Warren personally upheld the decision of an AEC official not to allow declassification of the secret Radiation Laboratory report on CAL-Z, on the grounds of possible embarrassment to the commission, despite the entreaties of Berkeley researchers.

Consent and Oversight

The history of human radiation experiments at the University of California indicates that different consent practices were followed at different times--reflecting, not surprisingly, the evolution of ethical and legal concerns about the rights of human subjects. In the case of patients receiving experimental radiophosphorus or radioiodine treatments at Crocker or Donner laboratories, for example, the fact that these patients were referred to Berkeley by other physicians at hospitals in the Bay Area suggests that they were probably provided with some explanation for the referral. It is not known however, what they were told, nor is there any record that bears on whether they formally consented to the subsequent procedure.

In all but one of the wartime and postwar plutonium and americium injections carried out at UCSF as part of the work done for the government under Contract 48A, no written record of consent could be found. Indeed, the memo of December 30, 1946, previously cited, suggests that the patients were deliberately not informed of the purpose or nature of the injection and a signed release was considered "invalid." It should be noted that classification rules alone cannot be considered a justification for this lack of disclosure, since, for example, the fact that plutonium consituted a principal ingredient in atomic bombs was no longer secret after publication of the Smyth Report in late August 1945.

Although no record of consent can be found in the case of CAL-1, Shields Warren subsequently recalled that in December 1947, Joseph Hamilton claimed that "he had explained to the patients that they would receive an injection of a new substance that was too new to say what it might do but that it had

some properties like those of other substances that had been used to help control growth processes in patients, or something of that general sort."[107] As discussed in chapter 5 of the Advisory Committee's final report, if this is what was said, it may well have had the effect of misleading patients into believing there was a potential direct benefit to them.

The only documentary evidence of consent in the medical file of CAL-2 is a standard form, "Consent for Operation and or Administration of Anaesthetic." Since this form contains no mention of experimental procedures and is dated May 2, 1946, or a week after CAL-2 was injected with radioisotopes, it evidently applied only to the biopsy, which was performed on May 3.

One of Hamilton's former associates, Patricia Durbin, has stated that she believes CAL-A's guardian was informed of the procedure followed in that case, but no evidence of consent could be found in the patient's incomplete medical file.[108]

In the July 1947 case of CAL-3, a written record by two physicians, attesting to the understanding and consent of the patient, fulfilled the recently established AEC requirements regarding consent. A proposed, more stringent regulation, requiring signed consent from the patient and recommended by the commission's lawyers, had been successfully resisted by AEC contractors in April 1947. As previously noted, however, the AEC also required that clinical testing must provide some potential benefit to the patient, a provision that was violated in the case of CAL-3.

One of the most striking aspects of the history of the human radiation experiments--at the University of California, as elsewhere--is the frequency with which the same individuals appear in the story, operating in different capacities and serving on various committees, but in the process exercising a degree of authority seemingly out of all proportion to their small number. Upon reflection, this phenomenon is attributable less to conspiracy (or coincidence) than to the simple fact that these few individuals represented almost the entire cohort of scientists who, in the early days of government-sponsored radiation research, possessed the combination of experience, training, and security clearances that allowed them to carry out this kind of work.

The same researchers who were among the most active in using human subjects for wartime radiation experiments were, by that very fact, deemed best able after the war to set the rules under which such experiments would be carried out, and even to approve the actual experiments proposed by them or their colleagues. In this role, for example, Joseph Hamilton served not only on the original Subcommittee on Human Applications of the AEC's Advisory Committee on Isotope Distribution, but likewise was a founding member of the local UC committee that reviewed radiation research on the Berkeley campus, to which the subcommittee had nominally given the responsibility for reviewing individual experiments. Two others who served with Hamilton on this UC committee, Stone and Miller, were acting simultaneously as both participant and overseer in human radiation research.

Inevitably, this interconnectedness led at least to the perception--and, sometimes, the reality--of a conflict of interest. As noted earlier, when DBM Director Shields Warren in early 1949 explicitly denied John Lawrence's request for carbon 14 to be used as a tracer in human subject research, Lawrence successfully appealed the decision to the Subcommittee on Human Applications, of which Joseph Hamilton was a founding member. Furthermore, Warren's pointed reminder to Lawrence several months later that the AEC had to approve the use of all isotopes, even those produced locally at the Rad Lab's cyclotron, and that "this procedure has not been uniformly followed in the past," suggests that the mechanisms the AEC had put in place to oversee the use of radioisotopes in human subject research were far from foolproof.

The duplication and diffusion of responsibility that marked the AEC's national supervision of radiation research were often replicated at the local level. University records indicate that UCSF and Berkeley's Donner Lab had separate committees to review proposals for the use of radioisotopes on human subjects. The Committee for the Safe Use of Radioisotopes, created at Berkeley in October 1946 at the instigation of President Sproul, had among its inaugural members Hamilton, Stone, and Miller.[109] The original purpose of this committee, however, was evidently to ensure the health and safety of campus researchers, not to safeguard human subjects used in research; to the extent that it also had responsibility for reviewing proposed human radiation experiments, that function was apparently auxiliary and came later.[110] By 1952, when the committee was reorganized at the urging of the AEC, its functions included oversight of proposals by campus researchers seeking AEC-supplied radioisotopes for their work.[111]

Evidence on the function of a "human use" committee at the Donner Lab remains sketchy, although a 1956 letter from John Lawrence to a UC colleague noted that such a committee had been functioning at the lab "for many years." The Donner Lab committee was evidently merged with the campus-wide safe use committee in 1958.[112]

In a January 1951 letter to the director of Highland-Alameda Hospital regarding safeguards on human subject research at the Donner Lab, John Lawrence gave "assurance that all of our investigations are approved by the National Isotope Committee of the Atomic Energy Commission and also by the local Radiation Laboratory Isotope Committee. Every investigation that we carry out on humans with radioactive isotopes is first approved by our local committee and then submitted to the National Committee for their approval, so that you can rest assured that any studies that we carry out on patients have this double protection."[113]

An undated draft of a "waiver policy" drawn up by John Lawrence, evidently from the early 1950s, relieved the Donner Laboratory, its physicians, and the university's Regents from liability should the patient become ill after receiving the "treatment previously discussed." In response to a 1952 query about consent policy at Berkeley, Lawrence wrote that no consent form was sought from paid volunteers.[114] This statement would appear to be consistent with the procedure followed in the 1949 and 1951 San Quentin experiments, which used paid prisoner volunteers. Oral consent was also apparently the standard in the earlier radioiodine studies at the Langley-Porter Clinic. In that case, however, the subjects also included patients described by the clinic's director as "severely schizophrenic," and hence presumably unable to make reasoned judgments concerning their own welfare.[115]

In addition to the Donner Lab and Berkeley campus-wide committees, a UC Regional Advisory Committee on Radiological Safety and a separate UCSF Committee on Clinical Use of Radioisotopes were also in existence by the early 1950s. While it is not known exactly when UCSF initiated a so-called human use committee concerning radioisotopes, records indicate that such a body was operating on the San Francisco campus in the early 1950s. Consent forms for the use of radioisotopes dating from 1952 have been located in UCSF medical records.[116]

By the late 1950s, consent policy at Donner Laboratory had evolved to a form signed by the patient, attesting that he or she had been apprised of the treatment and its possible side effects as well as anticipated benefits. The consent policy followed by UCSF at this time is not known in detail, but a 1959 letter from Robert Stone requested permission to discontinue use of consent forms for routine procedures involving the administration of radioactive isotopes, except where patients were under 21 years old.[117]

Whether consent was obtained in the case of CAL-Z and in subsequent zirconium and columbium injections is not known. Nor is it known what, if any, consent procedure was followed in the astatine

tracer study of the early 1950s. However, none of the surviving records in these cases include any evidence that written consent was obtained for the injection of an experimental radioelement.

In the 1960s, consent policy at the university followed guidelines established by the Public Health Service, and later by the Department of Health, Education, and Welfare. In February 1967, the Radiation Laboratory's Committee for Safeguards in Research in Human Subjects issued a statement of policy regarding research procedures involving human subjects. Henceforth, any studies done at Berkeley required presentation of a UC protocol, and those researchers receiving National Institutes of Health grants were to file a separate protocol with both the Rad Lab and NIH. All such studies also required written consent from the patient.[118]

In 1970, the president of UC extended the previously-established Public Health Service policy to all studies involving human subjects. The university updated its policies and procedures regarding studies involving human subjects in 1972. "Subjects" were defined as "any individual who may be at risk as a consequence of participation in research, development, demonstration or any other activities." Groups or individuals "with limited civil freedom," including prisoners, residents of institutions for the mentally retarded or mentally ill, and individuals subject to military discipline, were all identified as being "of particular concern."

CONCLUSIONS

The enlistment of the University of California in the war effort--and, in particular, the mobilization of the "Rad Lab"--is surely one of the most remarkable stories in the history of twentieth-century American science and technology. The fact that the university's president and the Regents' secretary-treasurer routinely committed the university to multimillion dollar contracts on the strength of verbal assurances from the Manhattan Project's director, General Groves, without knowing either the purposes or even the end product of this research, certainly represents a degree of trust between a public institution and the government that is foreign to the current day.

Both UC and the federal government clearly benefited from this collaboration: the university in the vastly increased support, financial and material, that it received for its programs and researchers; the government in the vast new wellspring of talent upon which it was now able to draw. However, this university-government alliance, despite its obvious advantages to both parties in the wartime emergency, and then during the Cold War, was not without costs.

For the university, the price of its alliance with the government was the sacrifice of meaningful oversight. Even well after the war had ended, when UC continued to administer three laboratories doing military-related research--Los Alamos, Livermore, and Berkeley's Rad Lab--major decisions as to support for particular classified programs were, in effect, simply delegated to the directors of those labs. This procedure followed the pattern established early on with the secret biomedical research conducted for first the Army and then the AEC.

Even when mechanisms for oversight were put into place, moreover, the ongoing feud between Berkeley's Division of Medical Physics and UCSF's Medical School suggest that they may have been pro forma at best and were in any case easily thwarted. On that point, it is important to realize that concerns about the university's complicity in ethically dubious radiation experiments on human subjects is not a matter of retrospective moral judgment, but rather was at the center of the Berkeley-UCSF feud of the 1940s and 1950s.

ENDNOTES

1. For example, Underhill, who negotiated the Los Alamos contract with the Army in February 1943, was not informed that the purpose of the project was to build an atomic bomb until the following November. Sproul evidently learned of its purpose even later. Interview, "Robert Underhill: Contract Negotiations for the University of California," Box 1, Robert W. Underhill papers, Bancroft Library, University of California.

2. Colonel O.G. Haywood to H.A. Fidler, 17 April 1947 ("Medical Experiments on Humans") (ACHRE No. DOE-051094-A-62), 1.

3. Numerous published accounts detail the pioneering role the University of California played in the history of nuclear medicine. See, for example, "How It Began" in Henry Wagner, Jr. (ed.), *Nuclear Medicine* (New York: HP Publishers, 1986); and John L. Heilbron and Robert W. Seidel, *Lawrence and His Laboratory: A History of the Lawrence Berkeley Laboratory* (Berkeley: Univ. of Calif. Press, 1989).

4. University Hospital and the Medical School were not known as the University of California, San Francisco campus (UCSF) until later. For the sake of continuity, however, the term UCSF is used throughout this chapter to refer to the UC hospital and medical school in San Francisco.

5. The war did not interrupt all clinical radioisotope research, however. Between 1942 and 1944, for example, at least eight UCSF patients with metastatic bone cancer were given radiostrontium as a therapy, a palliative, or in trace doses to determine update. Data on these patients was later classified and sent to the AEC as part of Project Sunshine, which sought to identify the danger of radiostrontium uptake from fallout. See Hamilton to Dunham, 6 April 1954. Also in 1942, Hamilton and John Lawrence reported on the first therapeutic use of radioiodine for the treatment of hyperthyroidism. Concerning this early history, see Joseph Hamilton, 1947 ("The Medical Application of Radioactive Tracers") (ACHRE No. DOE-072694-B-71); Robert Stone to Paul Aebersold, 25 April 1957 (ACHRE No. DOE-120994-B-2); and "Report on Donner Laboratory," November 16, 1962 (ACHRE No. DOE-121294-B-1).

6. S.H. Conner to John H. Lawrence, 30 September 1941("We recently had the pleasure...") (ACHRE No. DOE-122994-A-1).

7. Contract 36 outlined the terms under which the university agreed to administer Los Alamos. Contract 48 covered war-related work by personnel at Berkeley's Radiation Lab. The records for Contact 36 are held by the Los Alamos National Laboratory archives. Most of the equivalent records for Contract 48 are held at the National Archives and Records Center in San Bruno, California.

8. Joseph Hamilton to Robert Stone, 20 February 1943 ("Enclosed is an outline...") (ACHRE No. IND-071395-A-1).

9. On Stone's wartime work, see Barton Hacker, *The Dragon's Tail: Radiation Safety in The Manhattan Project* (Berkeley and Los Angeles, Calif.: UC Press, 1987), 30-31, 42; Col Kenneth Allen, ed., *Radiology in World War II* (Office of Surgeon Gen., Dept. of Army, 1966), 841-6; and L.F. Craver, "Tolerance to Whole-Body Irradiation of Patients with Advanced Cancer," in R. Stone, ed., *Industrial Medicine on the Plutonium Project: Survey and Collected Papers* (New York: McGraw-Hill, 1951), vol. 20: 485-98.

10. Robert Stone, 1 February 1948 ("Program and Budget Estimate for 1948-49, Health and Biology, Project NDP 48C") (ACHRE No. DOE-121294-B-4); see also Robert Stone to Alan Gregg, 4 November 1948 ("The candor of your letter...") (ACHRE No. UCLA-111094-A-25).

11. Concerning John Lawrence's wartime work in aeromedicine, see Hamilton, "The Medical Application of Radioactive Tracers," 7.

12. Mention that Berkeley's ROTC cadets volunteered for the aeromedicine study was made in an ACHRE staff interview with one of the investigators in that project. Cornelius Tobias, interview by Gregg Herken (ACHRE staff), transcription of audio recording, 23 March 1995 (ACHRE Oral History Project, Interview Program File, Targeted Interview Project).

13. On these early ideas for "rad warfare," see Barton Bernstein, "Oppenheimer and the Radioactive-Poison Plan," *Technology Review*, May/June 1985, 14-17.

14. Joseph Hamilton, 31 May 1943 ("A Brief Review of Possible Applications of Fission Products in Offensive Warfare,") (ACHRE No. DOE-072694-B-68).

15. Joseph Hamilton to Robert Stone, 20 February 1943.

16. Although Hamilton later reported that he was planning inhalation experiments involving human subjects, the only such experiment to come to light thus far involved Hamilton's assistant, Kenneth Scott, who voluntarily inhaled trace amounts of a short-lived isotope of radiozirconium in fall 1945. Kenneth Scott et al., 12 May 1945 ("Inhalation of Fissionable Materials and Fission Products and their Subsequent Fate in Rats and Man") (ACHRE No. DOE-120894-E-81).

17. Undated, "Summary of the Berkeley Project" (ACHRE No. IND-071395-A-11).

18. "Report of the UCSF Ad Hoc Fact Finding Committee on World War II Human Radiation Experiments," v. I, 23 (ACHRE No. UCSF-021095-A), 8. There has been confusion regarding the amount injected into CAL-1. According to Joseph Hamilton's reports, the patient was injected with 5 micrograms of a solution which combined Pu-238 and Pu-239. A re-examination of the data by Dr. Patricia Durbin, however, determined that the concentration of the solution was lower than Hamilton estimated, thus lowering the dose. R. E. Rowland and Patricia Durbin, "Survival, Causes of Death, and Estimated Tissue Doses in a Group of Human Beings Injected with Plutonium," *The Health Effects of Plutonium and Radium,* ed., Webster S. S. Jee (Salt Lake City, Utah: J.W. Press, 1976), 337. Reconstruction of doses for CAL-2 (2.683 micrograms) and CAL-3 (0.006 micrograms) track more closely with the original reports.

Concerning CAL-1, see the memo in ACHRE Briefing Book, October 1994, tab G. In an April 1946 report to the Army, Hamilton noted that "a very extensive study with plutonium 238 was undertaken employing a relatively normal human subject from whom several highly important tissue samples were secured including bone." Analysis of excreta from CAL-1 continued for more than a year. Ernest Lawrence Papers, Carton 5, "Cyclotron 60" 1946" folder, Bancroft Library, UC Berkeley. See also chapter 5 of the Advisory Committee's final report.

19. Joseph Hamilton, 14 September 1945 ("Progress Report for Month of September 1945") (ACHRE No. DOE-072694-B-69).

20. Joseph Hamilton to Col. Kelly, 28 August 1946 ("Summary of Research Program for Contract 48A") (ACHRE No. DOE-113094-A-8).

21. Joseph Hamilton to Col. Kelly, 28 August 1946.

22. Joseph Hamilton to Samuel Allison, 11 September 1945 ("Plans for Future Biological Research") (ACHRE No. IND-071395-A-2)

23. The original DMP proposed in 1944 ultimately became a branch of the Rad Lab headed by John Lawrence, later known as the Biomedical Division at the lab, but remained under the jurisdiction of the Berkeley Physics Department. It was the DMP that came into conflict with UCSF. On the creation of DMP, see the unpublished history of the Berkeley Physics Department by its longtime chairman, Raymond Birge, "History of the Physics Department, University of California, Berkeley," [manuscript], vol. V, 1942-50, pp. 51-3. According to Birge, the founding members of the Radiation Laboratory's Division of Medical Physics were John Lawrence, Joseph Hamilton, Cornelius Tobias, and Hardin Jones. In response to interest in the topic of human radiation experiments, there is now a history of the DMP, which remains unpublished as of this writing. See Peter Westwick, "Medical Physics at Berkeley, 1940-1950," draft mss., n.d. ACHRE staff are grateful to Mr. Westwick and the University for a copy of this manuscript.

24. Raymond Birge, "History of the Physics Department, vol. V", 52.

25. Cornelius Tobias, interview with Gregg Herken (ACHRE staff), transcription of audio recording, 23 March 1995, Eugene, OR (ACHRE Research Project Series, Interview Program File, Targeted Interview Project).

26. According to Birge, "A history of the Division of Medical Physics is not easy to write, primarily because of the friction that existed for many years between it and the Medical School. Regardless of the remarks by Dr. John Lawrence, which were accepted by the committee, it was obvious that the Administration of the Medical School felt strongly that all experimental work on *human beings* should be confined to the San Francisco campus .... How the committee was able to accept his remarks I have never understood, and the future struggles of Dr. Lawrence to gain permission to do certain work on human beings on the Berkeley campus indicated that the original permission could not have been very sincere." (Birge, vol. V., 53.)

27. On CAL-2, see memo in ACHRE Briefing Book, October 1994, tab G and chapter 5 of the Advisory Committee's final report.

28. In a January 1945 memo proposing experiments aimed at discovering the thyroid's tolerance for radioiodine, Stone suggested to Hamilton "that you could, through Dr. Soley, do some human studies along this line without exposing to him the reason for the studies being done at this time." Stone to Hamilton, 30 January 1945,

(On the occasion...") (ACHRE No. IND-071395-A-16). See also, Hamilton to Stone, 6 February 1945, ("I have made the necessary request...") (ACHRE No. IND-071395-A-3).

29. On CAL-2, see ACHRE Briefing Book, October 1994, tab G and chapter 5 of the Advisory Committee's final report. Simeon Shaw received 0.169 microcuries of plutonium 239 and unspecified, but presumably trace, amounts of cerium and yttrium.

30. In August 1945, a month before notifying the Army that he planned to do a second human subject experiment, this time using strontium, cerium and yttrium as well as plutonium, Hamilton reported at a meeting of MED's Health Division that he and his Berkeley colleagues were "carrying on studies using cerium and yttrium" in an effort to discover an isotope that penetrated to "the salt part of the bone." This work was apparently related to finding a chelating agent useful in removing plutonium from bone. See "Reports of the Various Laboratories to the X-10 Projects Advisory Committee, 21 August 1945 (ACHRE No. DOE-121494-D-3), 10.

31. In February 1995, the University of California issued its own three-volume report on the involvement of UCSF in human radiation experiments. That report notes that the differences between the three plutonium injections at UCSF "probably arise from an attempt by Hamilton and colleagues to piggyback two experimental designs...One satisfied the MED contract restrictions while the other satisfied their medical research interests." "Report of the UCSF Ad Hoc Fact Finding Committee on World War II Human Radiation Experiments," v. I, 23 (ACHRE No. UCSF-021095-A).

32. Loren J Larsen, 11 June 1946 ("To Whom It May Concern") (ACHRE No. IND-071395-A-4).

33. Hamilton to R. Ball 15 November 1946; K. Nichols to Berkeley Area Engineer, 24 December 1946 ("Reference is made...") (ACHRE No. DOE-113094-A-2). It is unclear from the documents whether the halt was ordered because of ethical objections to the experiments or because the work was outside the guidelines of those approved by the MED.

34. R. Ball to Hamilton, 12 February 1947 (Human Experiments) (ACHRE No. IND-071395-A-5).

35. John Burling to Edwin Huddleson, 7 March 1947 ("Memorandum of conversation") (ACHRE No. DOE- 120994-B-3); Carroll Wilson to Stafford Warren, 30 April 1947 ("This is to inform you...") (ACHRE No. DOE-072294-A-16). Wilson, who attended the early April meeting where future consent policy was evidently discussed, indicates in this letter that the topic may have been an issue of contention: "The Commission does not intend to influence in any way the exercise of judgment by the doctor as to the administration of any particular treatment authorized under the approved program. Indeed, from the discussion at the meetings of April 3-5, it seemed evident to me that doctors would not allow their judgment on this matter to be influenced by anyone."

36. Haywood to Fidler, 17 April 1947.

37. Carroll Wilson to Shields Warren, 30 April 1947.

38. Untitled, undated document by "K.G.S." [Kenneth Scott] (ACHRE No. UCLA-111094-A-1).

39. See ACHRE Briefing, October 1994, tab G concerning CAL-A and CAL-3.

40. T.S. Chapman to Berkeley Area Engineer, 30 December 1946 ('Human experiments") (ACHRE No. DOE-112194-D-3).

41. Hamilton to Paul Aebersold, 4 April 1946 ("I have spent some little time...") (ACHRE No. IND-071395-A-6).

42. Earl Miller, "Experience at the University of California with the Treatment of Patients with Hyperthyroidism by I131", UCRL-948, October 1950 (ACHRE No. DOE-113094-C-1).

43. Hamilton, n.d., ("Research Program--Contract 48--1947-48") (ACHRE No. NARA-082294-A-95). In a June 1945 memo to the Army concerning work being done for the Manhattan Project at Berkeley, Hamilton included "Iodine studies using radio-iodine as a tracer...The object here is to learn how best to block the up-take of radioiodine by prophylactic means." Hamilton to Fidler, 5 June 1945 (ACHRE No. IND-071395-A-17).

44. Hamilton to Fidler, 5 June 1945.

45. Earl Miller to Paul Aebersold, 14 April 1947 ("The following is for...") (ACHRE No. DOE-121294-B-3); Miller to Aebersold, 16 April 1948 (ACHRE No. DOE-121294-B-3).

46. Atomic Energy Committee, Subcommittee on Human Applications of Committee on Isotope Distribution, proceedings of 13 March 1949, revised minutes dated 19 July 1949 (ACHRE No. NARA-082294-A-24).

47. Concerning the NEPA program and Stone's role in the debate over human experimentation, see ACHRE Briefing Book, July 1994, tab G. See also chapter 8 of the Advisory Committee's final report.

48. See Stone, "Irradiation of Human Subjects as a Medical Experiment," in ACHRE Briefing Book, July 1994, tab G.

49. Joseph Hamilton, undated (A Report on the Past, Present, and Future Research Activities for Project 48-A-1") (ACHRE No. IND-071395-A).

50. Patricia Durbin, interview with Gregg Herken (ACHRE staff), transcription of audio recording, 11 August 1994, San Francisco, CA (ACHRE No. ACHRE-120194-A). It is also worth noting that another UCSF physician and former associate of Hamilton's, Dr. John Gofman, independently made the same point in a separate interview of the same date.

51. Robert Stone and Joseph Hamilton, untitled report, 31 May 1946 (ACHRE No. DOE-122494-A-1).

52. Joseph Hamilton to Dr. John Fulton, 19 July 1946 ("Inasmuch as both the Lawrence brothers...") (ACHRE No. DOE-122294-A-3); Hamilton, "The Medical Application of Radioactive Tracers".

53. Concerning the growth of federal, state, and private funding for UC cancer research at this time, see Dan Wilkes, "California vs. Cancer," *California Monthly*, April 1948, pp. 8-12; and Michael Shimkin, "How the University of California Wages Its Fight Against Cancer," *California Monthly*, February 1953, pp. 18-19. Grant applications from Stone, Low-Beer, John Lawrence, and other DMP researchers, as well as annual reports of the Cancer Project, are contained in the papers of the University President, Box 770, at the Bancroft Library, University of California, Berkeley.

54. Bertram Low-Beer, Ken Scott, Joseph Hamilton, and Robert Stone, 15 March 1948, "Comparative Deposition of Zr in a Reticulo- Endothelial Tumor to Normal Tissues in a Human Patient" UCRL-68 (ACHRE No. DOE-101194-B-4).

55. Albert Holland, Medical Advisor, Oak Ridge to Shields Warren, 9 August 1948 ("Review of Document") (ACHRE No. IND-071395-A-7).

56. Lawrence Berkeley Laboratory Archives and Records to Gregg Herken, ACHRE Staff, 20 January 1995, 4. These are notes taken on series CU-5, folder 140 at the Bancroft Library.

57. Medical record (incomplete), (ACHRE No. DOE-072694-B-72).

58. Stone and Low-Beer, "The Deposition of Radioactive Isotopes in Human Tumors," 8 March 1950, folder 140, "Applications," Box 770, University President papers, Bancroft Library.

59. Robert Stone, "Biological Effects of Radiations from External and Internal Sources" UCSF-1 (ACHRE No. DOE-51094-A-568) The comment by the Langley-Porter Clinic's director, Dr. I. Bowman, is in the transcript of a NEPA Report of 22 July 1949.

60. Contract 10 reads, in part: "This agreement recognizes that the University and the Commission are cooperating in a program of research and development related to atomic energy which has been carried on for more than five years by the Radiation Laboratory of the University at Berkeley under Contract [48]. The purpose of this agreement is to provide the means by which other divisions of the University, particularly in the San Francisco Bay area, may participate in the atomic energy program so as to encourage basic scientific progress and to assure adequate technical accomplishment in the interest of the national defense and public welfare." (Contract 12, establishing a similar relationship with the UCLA Medical School under Dean Stafford Warren, was signed the following month.) Regents Contracts, Box 11, folder 4, Bancroft Library, UC Berkeley.

61. John Lawrence, 16 November 1962 ("Report on Donner Laboratory,") (ACHRE No. DOE-121294-B-1).

62. Concerning a chronology of the battle between John Lawrence and the UC Medical School over the Metabolic Unit at Berkeley, see memo of 10/10/49 to Lawrence from Rad Lab administrator R. A. San Souci (ACHRE No. DOE-110894-A-1).

63. Francis Scott Smyth, Dean, to Robert G. Sproul, president, University of California, 7 February 1949 ("The experience thus far. . .") (ACHRE No. DOE-122294-A).

64. Robert G. Sproul, entry of 9 February 1949, Robert Sproul Papers, Bancroft Library, Box 2 "Confidential Memos 1946-1953", folder "1949 Memos".

65. "10 San Quentin Felons Used for Atom Tests," 12 April 1949, *San Francisco Examiner*. Tracer amounts of a short-lived radioisotope, Fe59, were used in the experiments.

66. Concerning radiation experiments involving other so-called captive or "vulnerable" populations, see the Advisory Committee's final report.

67. John Lawrence, undated ("History of Donner Laboratory") (ACHRE No. DOE-121294-B-8).

68. Lawrence wrote: "We do not ask for a signed statement and actually there has been not occasion to ask permission because any subjects (all 21 or over) not directly interested in the research are interested in a small remuneration..." J. Lawrence to G.E. Cartwright, 3 June 1952 ("We are grateful for the interest") (ACHRE No. DOE-122794-B-1).

69. Advisory Committee to the Division of Medical Physics, transcript of proceedings of 21 April 1953 (ACHRE No. DOE-121294-B-11).

70. This collaboration is detailed, for example, in the diary of Laguna-Honda's director, Dr. Michael Shimkin. See "Scrapbook of Laboratory of Experimental Oncology, 1947-54," UCSF archives.

71. "Laguna Honda Tumor Lab Opens on July 1," *San Francisco Call-Bulletin,* 28 June 1948.

72. K.G. Scott to C.L. Dunham, 21 October 1949 ("Owing to the absence...") (ACHRE No. IND-071395-A-8).

73. The consent form was criticized as "psychologically harmful" because it included a provision whereby the subject agreed to an autopsy at LEO in the event of his or her death. The Laguna-Honda director wrote a personal history of the controversy. See Shimkin, "Lost Colony: Laboratory of Experimental Oncology, San Francisco, 1947-1954," manuscript, Michael Shimkin papers, University of California, San Diego. Papers from the 1951 UCSF symposium were published in the February 27, 1953, issue of *Science.* Stone later objected to two of the experiments proposed at the LEO in 1952, citing the Nuremberg Code's prohibition of the use of human beings in medical experiments as the reason for his opposition. University of California, Cancer Board, proceedings of 21 May 1952 (ACHRE No. DOE-050895-A-1).

74. Robert Sproul, President, University of California to Wendell Stanley, Chairman, Adivsory Committee on Inter-Campus Medical Teaching and Research, 23 May 1951 ("In order to take full advantage...") (ACHRE No. DOE-110894-A-2).

75. Cornelius Tobias, interview by Sally S. Hughes, 7 July 1979, transcript of audiotape (ACHRE No. IND-071395-A), 49-50.

76. John Lawrence to C. Dunham, 25 November 1952 ("Following our telephone conversation...") (ACHRE No. DOE-122794-B-2). Ironically, Stone and Hamilton both privately opposed the Berkeley metabolic unit in letters to Smyth. Hamilton wrote: "The major issue, as it now stands, is the fact that practically all of the members of the medical school faculty feel that the proposed unit, as well as some of the present activities at the Donner Laboratory, do at present and will in the future subject both patients and normal individuals to undue risks when they are employed for experimental procedures. . .President Sproul should be made fully aware of the fact that if this situation is allowed to continue and expand that there is a grave possibility that there will be a serious accident." Hamilton to Smyth, 11 February 1949 ("After our brief conversation...") (ACHRE No. IND-071395-A-12).

77. John Lawrence to Charles Dunham, 25 November 1952.

78. Concerning this expansion, see Robert Stone, "The History of the Radiological Laboratory, 1942-1954," September 1954 (ACHRE No. DOE-110894-A-4).

79. Alan Gregg, Chairman, ACBM to Robert Stone, 20 October 1948 ("The secrecy with which...") (ACHRE No. UCLA-111094-A-24).

80. Shields Warren, diary excerpts, 23/24 April 1948, as typewritten by Gil Whittemore (ACHRE staff) (ACHRE No. BU-030395-A).

81. Shields Warren to A. Holland, 19 August 1948 ("Review of Document") (ACHRE No. DOE-051094-A-610)

82. Shields Warren to Robert Stone, 11 July 1949 ("I have delayed for some time...") (ACHRE No. IND-071395-A-13)

83. Warren Wrote in his diary: "John Lawrence asked for stilbamadine with C14--refused until meets regular standards." Shields Warren, diary excerpts, 12 January 1949, as typewritten by Gil Whittemore (ACHRE staff) (ACHRE No. BU-030395-A).

84. Hamilton served on this subcommittee. On its recommendation that Lawrence's request be granted, see AEC, Subcommittee on Human Applications, 19 July 1949 "Revised Tentative Minutes of March 13, 1949. . .".

85. Shields Warren to John Lawrence, 11 August 1949 (ACHRE No. IND-071395-A).

86. Widely misinterpreted as raising ethical objections to human experiments in this letter, Hamilton seems to in fact have been proposing such an experiment. Joseph Hamilton to Shields Warren, 28 November 1950 ("Unfortunately, it will not be possible...") (ACHRE No. IND-071395-A-9).

87. Concerning the "magic bullet" thesis and its possible applicability to the astatine experiment, see Advisory Committee on Human Radiation Experiments, Briefing Book #7, tab G.

88. Hamilton, Durbin, and Parrott, "Accumulation of Astatine211 by Thyroid Gland in Man," *Proceedings of the Society for Experimental Biology and Medicine,* vol. 86, 366-9. This report notes that the Isotope Unit at the Ft. Miley Veterans Administration Hospital was used for one of the astatine studies; a patient at the VA hospital was evidently one of the experimental subjects. A Berkeley researcher and colleague of Hamilton's, Dr. Patricia Durbin, has suggested that CAL-A and all but the first plutonium experiment may also have been "magic bullet" trials.

89. Cornelius Tobias, interview with Gregg Herken, 23 March 1995.

90. Joseph Hamilton to Walter Claus, Division of Biology and Medicine, 18 June 1954, ("Tuesday, June 15th, Dr. L Van Middlesworth...") (ACHRE No. IND-071395-A-10).

91. Claus to Hamilton, 30 June 1954 ("Many thanks for your letter...) (ACHRE No. DOE-032195-B-1).

92. John Lawrence, 1958 "Atomic Energy Commission Projects in Biology and Medicine at the University of California," (ACHRE No. DOE-121294-B-9), 2.

93. Robert Stone, "Radiological Laboratory--Progress Report for Period Ending Sept. 30, 1962;" Stone, "Radiological Laboratory, 1963 Annual Report" (ACHRE No. DOE-113094-C-2).

94. Paul Henshaw, 1 December 1959 ("Visits to the Laboratories of Dr. Robert S. Stone, Univ. of California, San Francisco (October 14, 1959)and Henry Kaplan, Stanford Univ., Palo Alto (October 15, 1959)") (ACHRE No. IND-071395-A-18).

95. Robert Stone, "Radiological Laboratory 1963 Annual Report," 2-3.

96. Larry McDonald, et al., "Delayed Radionecrosis of the Central Nervous System," *Semiannual Report: Biology and Medicine*, ed. John H. Lawrence, Fall 1967, 182.

97. J.L. Born, et. al, UCRL-8242, "Biological and Medical Studies with High Energy Particle Accelerators;" Larry McDonald, et. al., "Delayed Radionecrosis of the Central Nervous System;" Cornelius Tobias, et. al., UCRL-2907, "Irradiation Hypophysectomy and Related Studies Using the 340-MeV Protons and 190-MeV Deuterons;" John Lawrence, et. al., UCRL-10906, April 1963 "Heavy Particles, the Bragg Curve, and the Suppression of Pituitary Function in Diabetic Retinopathy". All of these were included in the Hamilton collection (ACHRE No. DOE-072694-B-73).

98. John Lawrence, et al. "Heavy Particles, the Bragg Curve and the Suppression of Pituitary Function in Diabetic Retinopathy," UCRL-10906, 4.

99. Levy received IRB approval and obtained informed consent to examine patient records. Thus far, he has examined the smaller cohorts which included patients with chromophobes, adenomas, prolactinoma, and Cushing's disease. Due to funding constraints, he has not yet examined the patient cohorts involving acromegaly, metastatic breast cancer, and diabetic retinopathy. Dr. Richard Levy, telephone interview with ACHRE staff, 12 April 1995.

100. H. D. Bruner, Assistant Director for Medical and Health Research, Division of Biology and Medicine to Drs. Hardin Jones and John Lawrence, Donner Laboratory, Univ. of California, 15 March 1962 ("A problem that is going to give everyone...") (ACHRE DOE-121294-B-2).

101. Details on the Diaper Study can be found in the Hamilton Collection. See, for example, Dr. Norman Telles, Div. of Radiological Health, Public Health Service to Dr. Robert Stewart, Nutritional Research Manager, Gerber Baby Foods, 16 May 1960 ("Due to the press. . .") (ACHRE No. DOE-072694-B-70).

102. John Lawrence to H.A. Gross, Chief Medical Officer, Neumiller Hospital, 30 March 1962 ("Please find enclosed...") (ACHRE No.DOE-121294-B-6)

103. H. A. Gross, Chief Medical Officer, Neumiller Hospital to F. R. Dickson, Warden, San Quentin Prison, 11 May 1962 ("Research Proposal") (ACHRE No. UCLA-111094-A-37)

104. Theo Miller, Medical Director, Napa State Hospital to John Lawrence, 2 June 1958 ("For several years now...") (ACHRE No. DOE-121294-B-5)

105. Stone suggested to Shields Warren that the danger of lawsuits could be avoided by the simple expedient of removing the initials of the patients from the wartime reports: "With the initials removed, there will be no means by which the patients can ever connect themselves up with the report." Stone to Warren, 6 October 1948 ("I have recently been shown...") (ACHRE No. DOE-120994-A-27).

106. Ibid.

107. AEC Division of Biomedical and Environmental Research and Division of Inspection, 13 August 1974 ("Disclosure to Patients Injected with Plutonium") (ACHRE No. DOE-051094-A-586)

108. Patricia Durbin, interview with Gregg Herken (ACHRE staff), 11 August 1994.

109. A letter from John Lawrence to Sproul indicates that the committee held its first meeting in November 1946. John Lawrence to Robert Sproul, 20 November 1946 ("The first meeting of the committee...") (ACHRE No. IND-071395-A-19).

110. There also remains some question as to how often this committee met, and how effective it was. In June 1948, for example, Robert Stone wrote to John Lawrence complaining, "Your letter gives the President the impression that we have had continuing meetings whereas no such meetings have been held." Robert Stone to John Lawrence, 15 June 1948 ("I have signed the letter...") (ACHRE No. IND-071395-A-20).

111. Hardin Jones to S. Alan Laugh, 30 January 1952 ("Applications for General Authorization for Procurement of Radioactive Isotopes to be Used in Humans") (ACHRE No. DOE-121294-B-10). Like the campus-wide committee on safe use of radioisotopes, there remains some question about the scope and authority of the Donner Lab human use committee. Thus, an undated memorandum titled "Clarification of Purpose and Functions of the Donner Laboratory Committee on the Safe Use of Radioisotopes in Human Subjects" notes, "The Donner Laboratory for 'Safe Use of Radioisotopes in Human Subjects' serves only in an advisory capacity. It has neither the responsibility, nor the authority, to interfere with experiments from which it has withheld approval." Saul Winchell, undated ("Clarification of Purpose and Functions of the Donner Laboratory Committee on the "Safe Use of Radioisotopes") (ACHRE No. DOE-042495-A-1).

112. Lawrence's letter is cited in a UC report, "Re: Protection of Human Subjects," 24 May 1974 (ACHRE No. DOE-121294-B-12).

113. John Lawrence to Otis Whitecotton, Director, Highland-Alameda County Hospital, 10 January 1951 ("Dr. Robert Parsons is going to explain...") (ACHRE No. DOE-113094-C-3).

114. John Lawrence to G.E. Cartwright, College of Medicine, Univ. of Utah, 3 June 1952 ("We are grateful...") (ACHRE No. DOE-122794-A-1).

115. NEPA Medical Advisory Panel, Subcommittee No. IX, proceedings of 22 July 1949 (ACHRE No. DOD-121494-A-2).

116. "Response to the Presidential Advisory Committee Request for University of California Documents ACHRE Request 102494-A", 1.

117. R. Stone to John Adams, 14 April 1959.

118. Committee for Safeguards in Research in Human Subjects, "Statement of Policy of the Berkeley Lawrence Radiation Laboratory," February 1967. (ACHRE No. DOE-110894-A-3).

3

CURRENT FEDERAL POLICIES GOVERNING HUMAN SUBJECTS RESEARCH

This chapter supplements chapter 14 of the committee's report on current federal policies governing human subjects research. Here we describe the administrative structures and procedures for ensuring compliance with federal rules for the protection of human research subjects currently employed by six departments and agencies: the Department of Health and Human Services (DHHS), the Department of Defense (DOD), the Department of Veterans Affairs (VA), the Department of Energy (DOE), the National Aeronautics and Space Administration (NASA), and the Central Intelligence Agency (CIA). In addition, this chapter provides summary information on ten additional federal departments and agencies that sponsor and/or conduct research involving human subjects (see table 1 at the end of this chapter). We asked each of the six agencies to provide information on the following:

- the scope of its human subjects research programs;
- the organizational structure of its human subjects protection efforts and the resources devoted to such activities;
- the policy issuances and guidances pursuant to the Common Rule[1] that the agency has provided to subsidiary agencies and research institutions;
- monitoring and enforcement activities;
- sanctions available for noncompliance with human subjects protections;
- the existence of and rules governing classified research involving human subjects; and
- the use or potential use of waivers of any of the requirements of the Common Rule or the agency's own human subjects regulations.

The information presented below is based largely on this survey.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

DHHS is the federal department with the largest presence in biomedical and behavioral research involving human subjects, approximately $2.8 billion annually.[2] The following agencies of the Public Health Service (PHS, a component of DHHS) conduct most of the DHHS-sponsored biomedical and behavioral research: the National Institutes of Health (NIH, consisting of twenty-four separate institutes and centers), the Centers for Disease Control and Prevention, the Health Resources and Services Administration, the Indian Health Service, the Substance Abuse and Mental Health Services Administration, and the Food and Drug Administration. DHHS-supported behavioral research is conducted by other agencies as well, including the Office of the Secretary, the Health Care Financing Administration, and the Administration for Children and Families.

In addition to supporting a limited number of intramural and extramural research activities that involve human subjects, FDA also regulates all research, whether sponsored by public or by private entities, that is used in support of new drug, biologics, and device applications.[3] Because the statutory basis for FDA regulation of research on drugs and devices is separate and distinct from that for DHHS-supported and conducted research, FDA rules and oversight practices differ in certain respects and are discussed in a separate section below.[4]

DHHS Authority for the Protection of Human Subjects

Amendments to the Public Health Service Act in 1974 (Public Law 93-348), 1985 (P.L. 99-158), and 1993 (P.L. 103-43) provide the current statutory basis for the human subjects protections afforded by DHHS research programs. The 1985 Health Research Extension Act directs the secretary to require that each institution applying for a grant, contract, or cooperative agreement for research involving human subjects provide assurances that it has established an institutional review board (IRB) to review such research, in order to protect the rights and welfare of the subjects of the research. It further directs the secretary to establish a program to respond to requests for guidance regarding ethical issues raised in the course of research and to establish a process for responding to information provided to the director of NIH regarding violations of the rights of human subjects of research funded under the Act. The 1993 NIH Revitalization Act strengthened these requirements by making IRB review, and approval by a majority of IRB members, a prerequisite to any DHHS funding of the research.

Additional Provisions of the DHHS Regulation

In addition to the Common Rule, which is reflected in subpart A of 45 CFR Part 46, Protection of Human Subjects, the DHHS regulation includes subpart B, for research involving pregnant women, fetuses, and *in vitro* fertilization; subpart C, governing research involving prisoners; and subpart D, governing research involving children.

Subpart B authorizes the secretary of DHHS to establish one or more Ethics Advisory Boards (EABs) to advise on ethical issues raised by individual research proposals that involve pregnant women, fetuses, and *in vitro* fertilization.[5] Such a board may also establish certain classes of research that require EAB review and approval prior to departmental funding.[6] Subpart B limits research activities involving pregnant women, fetuses, and *in vitro* fertilization to those that (1) are conducted only after appropriate studies with animals and nonpregnant women; (2) involve only minimal risk to the fetus, unless the activity is for the benefit of the particular pregnant woman or fetus; (3) preclude the involvement of the researchers in any decisions about terminating a pregnancy or determining the

viability of the fetus; and (4) prohibit any research intervention involving greater than minimal risk to the pregnant woman or fetus as part of any procedure for terminating the pregnancy.[7] Informed consent must be given by legally competent parents, except that the consent of the father is not required under certain circumstances.[8]

Research activities directed towards fetuses *ex utero* are limited to those that (1) pose no added risk to the fetus and are for the purpose of developing important biomedical knowledge not obtainable by other means, (2) enhance the possibility of survival of the particular fetus, and (3) neither artificially maintain the vital functions of the fetus nor terminate its heartbeat or respiration. The informed consent of parents is likewise required for research involving fetuses *ex utero*.[9]

Subpart B directs IRBs to determine that all aspects of the research activity meet these requirements and to give particular attention to the procedures for the selection of subjects and the monitoring of the informed consent process.[10] It also gives the secretary authority to modify or waive its specific requirements, with the approval of the EAB, after concluding that "the risks to the subject are so outweighed by the sum of the benefit to the subject and the importance of the knowledge to be gained as to warrant such modification or waiver."[11]

Subpart C provides additional protections for prisoners involved as subjects in behavioral and biomedical research, because of the concern that incarceration may affect the ability of prisoners to make a truly voluntary decision about participating in such research. In addition to the requirements of the Common Rule, IRBs must ascertain that participation offers no excessive advantages that would distort a prisoner's decision to participate, that the risks are commensurate with risks that would be accepted by a nonprisoner population, that selection procedures among prisoners are fair, that control subjects are randomly selected, and that follow-up care or examination will be provided.[12]

Research involving prisoners is required to pertain only to those topics that are particularly relevant to the lives of prisoners, such as studies of the causes, effects, and processes of incarceration and criminal behavior; research on conditions particularly affecting prisoners as a class, such as alcoholism and drug addiction or hepatitis vaccine trials; or research that is intended and likely to improve the health and well-being of the subject.[13] A majority of the members of any IRB (exclusive of prisoner members) that reviews research proposals involving prisoners must have no association with the prison(s) involved, apart from their membership on the IRB. At least one member must be a prisoner or a prisoner representative.[14]

Subpart D provides additional protections for children involved as subjects of research. It requires that IRBs approve research involving children only if the research meets the following additional conditions: (1) the research involves no more than minimal risk and researchers obtain the child's assent, meaning the child's affirmative agreement,[15] in addition to the parents' permission; (2) the research involves greater than minimal risk but presents the prospect of direct benefit to the subjects; or (3) the research is not of direct benefit and involves greater than minimal risk to the subject but is likely to yield generalizable knowledge about the subject's disorder or condition.[16] If the IRB finds that proposed research does not meet these three conditions, DHHS may still conduct or fund the research if the secretary, after consulting with experts and after public review and comment, determines that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting children, that the research will be conducted in accordance with sound ethical principles, and that adequate provisions are made for soliciting the assent of children and the permission of their parents.[17]

Responsibility for Human Subjects Protections Within DHHS

DHHS oversight of human subjects protections for the research that it conducts or supports is the responsibility of the Office for Protection from Research Risks (OPRR), located within NIH. OPRR develops and interprets DHHS policies on human subject protections, provides guidelines for research institutions and IRBs, cosponsors workshops with FDA to educate IRB members and staff (four or five per year, involving 100 to 200 persons each), and negotiates and approves "assurances of compliance" (discussed below) with research institutions.[18] It also investigates claims of noncompliance with these rules. In addition, the director of OPRR chairs the Interagency Human Subjects Research Subcommittee of the Health, Safety, and Food Research and Development Committee of the National Science and Technology Council, which is responsible for ensuring the uniform interpretation of federal policy for human subjects research.[19]

OPRR currently has 14 staff members and an annual budget of approximately $1 million devoted specifically to human subjects protection. An additional 76 full-time-equivalent staff (FTEs) in other parts of PHS contribute to human subject protection policy and oversight activities.[20]

Policies and Practices in the Oversight of Human Subjects Research

The written assurances of compliance that OPRR negotiates with institutions such as universities, hospitals, and independent research facilities, as well as research components within DHHS, are the basic mechanisms for the enforcement of human subjects protections. An assurance of compliance commits an institution and its personnel to full adherence with the DHHS human subjects protection regulations. The nation's largest research institutions have negotiated multiple project assurances (MPAs) with OPRR. MPAs can cover a comprehensive array of research activities involving human subjects and are generally in effect for a five-year period.[21]

As part of its assurance of compliance, a research institution is required to state the principles governing its activities for protecting the rights and welfare of human subjects, to make a commitment to adhering to the provisions of DHHS human subjects regulations for all federally funded research, and to describe its practices for protecting human subjects, including the policies and procedures of its IRB.[22] Ninety-three percent of all research institutions that have negotiated MPAs with OPRR have voluntarily agreed to extend the specific protections of the DHHS regulation to research that is not federally supported.[23] Approximately 420 institutions currently have 453 MPAs with OPRR. In addition, there are about 3,000 single project assurances (SPAs) governing the conduct of human subjects research in smaller, newer, or primarily clinical settings; 1,173 cooperative project assurances; and 1,436 noninstitutional investigator agreements. These investigator agreements, negotiated by OPRR with individual clinicians involved in cooperative studies and large clinical trials, are additional to a project assurance for the overall study. Four full-time OPRR professionals are responsible for soliciting and managing the more than 6,000 assurances of all kinds that are currently in effect.[24]

Every application to DHHS for a grant, contract, or cooperative agreement is reviewed by the funding entity to ascertain whether human subjects are involved in the proposed research, to determine whether the applicant has received IRB approval for the proposed research, and to make an independent assessment of human subjects risks and protections. This evaluation is followed by additional review through peer review for technical and scientific merit. Concerns with the adequacy of human subjects protections or potential risks, or a need to review further documentation, (such as the informed consent form itself), is noted in the summary statement on scientific merit and will become part of the application file. The scientific review group notifies not only OPRR but also the national advisory

councils (through the summary statements) of its concerns regarding the involvement of human subjects in grant applications that it has reviewed. These concerns must be resolved by the investigator or institution proposing the research prior to any funding of the project.[25] If the institution proposing the research does not have an MPA of the necessary scope on file, OPRR negotiates a single project assurance before the research activity is funded. OPRR does not otherwise routinely review individual research protocols for compliance with human subject protections.[26]

Once institutional assurances of compliance have been approved, OPRR oversees the conduct of human subjects research primarily on an exceptions basis--that is, in cases where questions or complaints have been raised or when adverse outcomes are reported. OPRR does not routinely audit IRB records, nor does it interview research subjects to ascertain that appropriate procedures have been followed. It does, however, follow up on reports from institutions or investigators; complaints from research subjects, patients, or the public; and information forwarded by FDA or other agencies. Such information may be about adverse outcomes within the context of research, or about incidents of noncompliance with regulations or with the terms of the particular institutional assurance or approved research protocol.[27]

Certain kinds of research supported or conducted by DHHS are followed and reviewed more closely with regard to the experience of patient-participants. For example, Cooperative Oncology Group (COG) research supported by the National Cancer Institute (a component of NIH) is monitored with on-site audits that include an evaluation of human subjects protections.[28] Some NIH-supported multicenter clinical trials are monitored by independent data and safety monitoring boards (DSMBs) that assess emerging data to ensure subject safety and the relative efficacy of alternative treatments.[29] The outcomes data reviewed by DSMBs might not be readily accessible to IRBs and participating clinicians, and DSMBs are not directly accountable to local IRBs or OPRR. However, the principal investigator is required to report to the IRB at regular intervals, and it is the principal investigator who receives information from the DSMB on, (among other things), concerns related to risks to patient-subjects.

IRBs are required not only to review and approve all proposed research involving human subjects in advance of its funding by a federal agency, but also to conduct reviews during the course of the research at intervals appropriate to the degree of risk involved, but at least annually.[30] OPRR is placing increased emphasis in its guidance to IRBs on the importance of continuing reviews.[31]

OPRR estimates that about half of the reports of incidents or compliance issues that it receives are self-reports from the research institution, either by the investigator, the IRB, or other responsible official. During the period 1990-1994, OPRR initiated investigations of 249 reports of potential noncompliance or problematic situations and had completed 152 of them as of December 31, 1994. During the same period, OPRR reviewed an additional 462 reports, (including 191 institutional incident reports, over 200 FDA inspection reports, and 40 unsubstantiated allegations) for which it determined that no investigation was necessary.[32] Most compliance oversight investigations are conducted through correspondence with the institution and do not require an on-site review.

Complainants generally receive information about the outcome of OPRR's investigation at the completion of an oversight investigation. Once an investigation is completed, the final report of findings by OPRR becomes publicly available under the Freedom of Information Act (FOIA), along with related documents.[33] In 1993, OPRR filled 32 FOIA requests related to human subjects protection compliance reviews; in 1994, 54 such requests were filled.[34] Ordinarily there is no official announcement of a compliance review.

At any time during an investigation, OPRR may suspend an institution's assurance concerning some or all research activities. If this occurs, the affected research projects cannot be supported by any

DHHS component until an appropriate assurance is again approved by OPRR. Other steps that OPRR might take consequently to a compliance investigation are:

- requiring revisions to the informed consent document or process;
- requiring prior OPRR review of some or all research projects;
- requiring that investigators receive education in human subjects protection;
- requiring special reporting to OPRR;
- recommending to DHHS that an institution or investigator be temporarily suspended or permanently removed from participation in specific projects; and
- recommending to DHHS that an institution or investigator be declared ineligible to participate in DHHS-supported research (debarment).

Debarment or suspension of a participant in a federal program by one agency has government-wide effect.[35]

Waivers from Provisions of the DHHS Regulation

The secretary of DHHS has authority to grant waivers from the requirements of the department's human subjects protections regulation, including the requirements for informed consent.[36] The single secretarial waiver to date was from the requirement for local IRB review in the case of the investigational drug d4T, used in the treatment of AIDS patients.[37] FDA's "parallel track" policy permits expanded availability of investigational new drugs for AIDS/HIV patients who are not able to take standard therapy, or for whom standard therapy is no longer effective, and who are unable to participate in ongoing controlled clinical trials. Under this policy, patients may be given promising investigational drugs, concurrent with the conduct of controlled trials. Because it would be difficult for local IRBs to oversee and approve the participation of clinical groups, and for individual practitioners not ordinarily involved in research to obtain local review, FDA is using an NIH IRB in lieu of local IRB review.[38]

FOOD AND DRUG ADMINISTRATION

As a subagency of DHHS, FDA is subject to the DHHS regulation for human subjects research that it conducts or financially supports. However, for human subjects research involving products regulated by FDA, separate rules under the statutory authority of the Food, Drug, and Cosmetic Act apply. When research involving products regulated by the FDA is funded by DHHS, both DHHS and FDA regulations apply.[39]

FDA Authority for the Protection of Human Subjects

The Food, Drug, and Cosmetic Act directs FDA to ensure the protection of the rights and welfare of human subjects who participate in clinical investigations of new drugs, biologics, and devices, food and color additives, and electronic products, and in clinical investigations that support applications for research or marketing permits for products regulated by FDA.[40] The regulations governing the conduct of human subjects research that FDA regulates are codified at 21 CFR Part 50 (Protection of Human Subjects) and 21 CFR Part 56 (Institutional Review Boards). These regulations are the same as the DHHS regulations in most respects but include several significantly different

substantive provisions. Specifically, FDA uses different criteria for an exception to informed consent, and FDA provides for a waiver of IRB review only in emergency situations.[41] Furthermore, FDA does not use institutional assurances of compliance, relying instead on its bioresearch monitoring program.[42]

Responsibility for Human Subjects Protections in Research Involving Products Regulated by FDA

FDA's Bioresearch Monitoring Program involves on-site inspections of nonclinical laboratories, IRBs, study sponsors (e.g., pharmaceutical companies), and clinical investigators to assure the protection of human subjects and the integrity of data reported to FDA. Each operational component of FDA (drugs, biologics, devices) has such a monitoring unit.[43]

Policies and Practices in the Oversight of Human Subjects Research

FDA reasoned (in the *Federal Register* announcement of the Common Rule) that establishing an assurance system geared to those IRBs that are exclusively subject to FDA regulation would result in "increased administrative burdens" that would not be justified by the benefits; FDA would therefore continue to rely on its Bioresearch Monitoring Program, along with educational activities, to achieve IRB compliance.[44] Under its monitoring program, FDA inspects IRBs routinely every five years and, in addition to its own sanctions, reports any findings of noncompliance to OPRR for independent action if the IRB in question holds an OPRR-approved assurance.[45]

An FDA inspection involves a site visit and a standardized review of the documentation maintained by the IRB. FDA sends regulatory letters to IRBs after site visits, reporting its findings and specifying corrective actions that must be taken. IRBs with substantial compliance violations are usually reinspected within a year's time. FDA inspects over 600 clinical investigators, 270 IRBs, 60 sponsors, and 120 nonclinical laboratories each year.[46]

FDA requires IRBs to conduct continuing (no less than annual) review of ongoing research. Continuing reviews must gather information on the number of subjects initiated into research, describe research subjects' experiences in terms of benefits, identify adverse effects and withdrawals from the project, report on research results, and provide an updated risk-benefit assessment. When unanticipated risks or information bearing on the risk-benefit assessment of the research are discovered, they must be reported to the IRB promptly.[47]

FDA regulations allow research sponsors and investigators to request a waiver of the requirement for IRB review of research, but not of the requirements for informed consent of subjects.[48] This provision is intended for use "only where it would be in the best interest of the subjects and where alternative mechanisms for assuring the protection of the subjects are adequate"[49]--for example, in the case of treatment investigational new drugs for persons with serious or life-threatening diseases.

FDA has distinctive sanctions against noncompliant IRBs and research institutions. If IRBs and institutions refuse FDA access to IRB records for inspection, FDA may disqualify the evidence provided from a study in support of an application for an FDA research or marketing permit for a new drug or device.[50] If during an inspection an IRB is found to be in noncompliance, FDA may:

- reinspect the institution to confirm that corrective measures have been taken;
- withhold approval of any new studies conducted by the institution or reviewed by the IRB;
- direct that no new subjects be added to ongoing studies;

- terminate ongoing studies;
- notify other state or federal regulatory agencies or parties with a direct interest in FDA's action; and
- disqualify the IRB or parent institution, which may entail a refusal to consider data from a clinical investigation offered in support of a marketing permit.[51]

FDA Exception from the Requirement for Informed Consent

Some medical speciality groups have advocated an exception from informed consent in the case of emergency research (i.e., medical interventions under a research protocol) so that advances can be made in such treatments for patients unable to give consent, such as those unconscious with head trauma, spinal cord injury, or stroke.[52] However, the necessary randomization of treatment alternatives under such emergency conditions is problematic under both the FDA regulation and the Common Rule.

FDA rules allow for administration of a test article, (that is, an investigational drug, biologic, or device), if (1) the subject is confronted by a life-threatening situation necessitating the use of the test article, (2) informed consent cannot be obtained from the subject, (3) time is not sufficient to obtain consent from the subject's legal representative, and (4) no alternative method of approved or generally recognized therapy exists that provides an equal or greater likelihood of saving the subject's life. The use of this test article under these circumstances must be reported to the IRB within five days.[53] This provision, however, did not anticipate a research situation in which subjects (patients) would be randomly assigned to different treatments and in which the experimental treatment would be used repeatedly without informed consent, as would be the case for research on investigational interventions used in the care of unconscious patients or for patients whose ability to give consent is otherwise compromised. At the time of this writing, the FDA had proposed new regulations for conducting research in emergency settings. It is expected that the new regulations will be promulgated by the end of 1995.

In contrast, the Common Rule for federally funded research directs that, if a test article is used for emergency treatment without informed consent, data gathered or information resulting from that case cannot be used in any study or scientific report about the test article.[54] The Common Rule permits the IRB to waive the requirement for informed consent if, among other things, the research involves no more than minimal risk to the subjects. Because the purpose of this emergency research is to determine the risks and benefits of the intervention--that is, its safety and effectiveness--it is difficult to judge whether the risk of the research is minimal or greater than minimal. Furthermore, if the risk is judged to be greater than minimal, but is offset by even greater potential benefits to the subject, there is no provision in the Common Rule that would permit an IRB to waive informed consent.

DEPARTMENT OF DEFENSE

DOD conducts biomedical and behavioral research involving human subjects within each of its services (Army, Navy, and Air Force). Several additional DOD agencies, such as the Uniformed Services University of the Health Sciences (USUHS), fund biomedical research through the services. In addition to mission-specific research, DOD engages in research projects mandated by Congress, such as its women's health and breast cancer research programs. Some clinical research within DOD facilities is sponsored by other federal agencies or by private entities.[55] DOD sponsors human subjects research through two separate programmatic and funding authorities, its clinical research program and its research

and development (R&D) program. The clinical research program largely takes place within DOD medical facilities and is focused on traditional biomedical research topics. DOD's R&D program addresses a broader range of biomedical and behavioral research questions of particular or unique relevance for the military mission, for example, studies of human safety factors in the development of new weapons systems.

DOD Authority for the Protection of Human Subjects

A statutory basis for informed consent was provided by the Defense Department Authorization Act of 1985, which directs that:

> Funds appropriated to the Department of Defense may not be used for research involving a human being as an experimental subject unless--
> (1) the informed consent of the subject is obtained in advance; or
> (2) in the case of research intended to be beneficial to the subject, the informed consent of the subject or a legal representative of the subject is obtained in advance.[56]

DOD has codified the Common Rule at 32 CFR Part 219. In addition, DOD directives require conformance with subparts B, C, and D of the DHHS regulation, which address research involving pregnant women, fetuses, and *in vitro* fertilization; prisoners; and children, respectively.[57]

Responsibility for Human Subjects Protections Within DOD

Responsibility for oversight of human subjects protections resides with the director of the Office of Defense Research and Engineering. Operational oversight is delegated to the individual services or DOD agencies. Both research and development (R&D) projects and clinical investigation efforts come under the purview of the services' surgeons general.[58] In all, DOD devotes an estimated 80 full-time equivalents to assurance and compliance activities for protecting human subjects. This includes staff resources devoted to review and documentation of human subjects protection activities (excluding those of IRBs themselves) at all levels of the department.[59]

The primary responsibility for oversight of intramural clinical research rests with each hospital commander whose facility sponsors a clinical investigation program. This oversight is exercised primarily through the chief of the department of clinical investigation at each major teaching facility, primarily hospitals. Medical monitors are appointed for each study that involves more than minimal risk, to ensure the ongoing protection of human subjects involved in each project. The Human Use Committee (the facility's IRB) conducts annual reviews of each protocol involving human subjects according to the provisions of the Common Rule.

Within DOD's biomedical R&D programs, the commanding officers of the medical research laboratories and institutes are ultimately responsible for local institutional oversight. The principal committees within each research institution for review of protocols for scientific merit and the adequacy of protections for human subjects are the scientific review and the human use committees, this latter committee being the IRB. Human use committees conduct annual reviews of each protocol, in accordance with the provisions of the Common Rule.[60] A locally assigned physician serves as a medical monitor for each protocol determined to be of greater than minimal risk, as determined by the human use committee.[61]

More than 50 freestanding DOD facilities may conduct or contract for research involving human subjects. Within the Army, the Medical Research, Development, Acquisition, and Logistics Command at Fort Detrick, Maryland, oversees protocol reviews with regard to human subjects protections for all intramural and contract biomedical research. Within the Navy, both the Naval Medical Research and Development Command at the National Naval Medical Center, Bethesda, and the Office of Naval Research support human subjects research activities. Each of these operations is responsible for oversight of human subjects protections for research that they conduct or sponsor under contract. The Air Force facility most heavily involved with human subjects research is Armstrong Laboratory at Brooks Air Force Base, Texas. Human subjects protection coordination for Air Force R&D facilities is provided by the Headquarters Air Force Medical Operations Agency, Office of the Surgeon General. Within USUHS, its Research Administration coordinates the review and oversight of research protocols by the university's IRB.[62] DOD also maintains seven medical research laboratories overseas. The primary focus of the human subjects research conducted by these facilities is epidemiological surveillance of infectious diseases, field trials of vaccines and therapeutic drugs, and field validation of rapid diagnostic technologies.[63]

All human subjects research conducted by or sponsored extramurally by DOD must be conducted by an institution with a current project assurance, either an MPA issued by OPRR or an assurance issued by a military service or agency. For in-house research, the Director of the Office of Defense Research and Engineering has delegated responsibility for management and oversight of the issuance of project assurances to the director of the office of environmental and life sciences. This office provides policy guidance and maintains information regarding the project assurances issued by the agencies and services that conduct or support biomedical and behavioral research projects.[64]

Policies and Practices in the Oversight of Human Subjects Research

DOD reports that service headquarters provide continuous monitoring and audit reviews of the programs under their jurisdiction for compliance with human subject protections. The Office of the Surgeons General for each of the services determines whether additional administrative review of proposals involving more than minimal risk is warranted. They may provide such second-level review in a variety of ways, including using joint-service committees.

The services conduct announced and unannounced site visits to their own facilities to evaluate program management and to determine compliance with regulations. Between 1992 and 1995, the services have conducted approximately 180 site visits to facilities conducting research involving human subjects.[65] Headquarters offices ensure that adequate records of all research protocols are maintained at the research facility, that approved informed consent forms have been used and maintained, that progress reports have been filed, and that minutes of IRB meetings are maintained. Annual audit reviews of research protocols involving human subjects are conducted by the sponsoring agency or service. All reviews, audits, and site visits are documented. Permanent records of such audits or reviews are maintained by the office conducting or directing the audit.[66]

A 1987 memorandum of understanding states that DOD will comply with FDA regulations on the clinical testing and use of investigational drugs, acknowledges the need for expeditious FDA review of products that are needed to accomplish DOD's mission, and makes special provisions for security in FDA's review of clinical testing within DOD that is classified for reasons of national security.[67]

DEPARTMENT OF VETERANS AFFAIRS

VA operates 171 inpatient medical centers, including short-term hospitals, psychiatric and rehabilitation facilities, and nursing homes. It also operates a number of freestanding outpatient clinics.[68] VA's biomedical research and development program focuses on the health care needs of veterans. This research is almost exclusively intramural, although in limited instances (e.g., at congressional direction, or when an investigator needs specialized services) biomedical research is performed under contract.[69]

VA's research appropriation supports approximately 2,000 investigators who conduct about 12,000 discrete projects in VA facilities annually. A quarter of these projects are VA-funded, another quarter to a third are extramurally funded, and the remainder are conducted by VA personnel without specific research funding. VA spends approximately $114 million annually in appropriated monies on human subjects research; an additional $110 million of VA clinicians' time is devoted to research activities. Other federal agencies provide roughly $170 million annually for research in VA facilities, most of it clinical research, and an additional $100 million worth of research is conducted in VA facilities by private nonprofit and proprietary entities, such as the American Heart Association and pharmaceutical firms.[70]

VA Authority for the Protection of Human Subjects

The Common Rule is codified for VA at 38 CFR Part 16. In addition, 38 USC 7331 and 7334 require that all medical and prosthetic research conducted by VA occur only with the informed consent of subjects and that regulations governing human experimentation be coordinated with those of DHHS.[71]

Responsibility for Human Subjects Protection Within VA

Within the Veterans Health Administration (VHA), the Office of the Assistant Chief Medical Director for Research and Development is responsible for the overall planning, coordination, and direction of R&D activities. VHA's research program encompasses three areas: medical research, health services research and development, and rehabilitation research and development. Each research component is responsible for VA Central Office (VACO) review of research proposals for both scientific merit and the adequacy of human subjects protections. For the most part, oversight of human subjects protection takes place at the local medical facilities .[72]

The VA National Bioethics Committee is a 20-member advisory panel that meets twice yearly to advise the VA chief medical director and his staff on ethical issues in clinical care, resource allocation, and biomedical research within VA facilities. In 1991, VA established a National Center for Clinical Ethics under contract with the clinical ethics group at the VA Medical Center in White River Junction, Vermont, to serve as staff to the National Bioethics Committee and to enhance the quality of clinical ethics programs at VA medical centers. This center has, to date, worked mainly in areas other than human experimentation, instead focusing on clinical practice and resource allocation issues.[73] The center will likely become involved in issues entailed by human subjects research in VA facilities in the future.

Policies and Practices in the Oversight of Human Subjects Research

All research associated with VA facilities or VA clinicians, whether or not it receives research funding, is subjected to the same local review, approval, and documentation requirements. All human subjects research conducted in VA facilities or with VA monies is performed subject to the provisions of

the Common Rule. For the most part, individual medical facility staff members generate research proposals and submit them to institutionally based research and development committees. In some cases, however, research priorities are set by legislation, as in the case of HIV/AIDS research, alcoholism and drug dependency, spinal cord injury, and post-traumatic stress disorders. Individual VA medical institutions have R&D committees that review investigator-initiated research proposals. These committees have human studies subcommittees, which serve as the institutions' IRBs, as well as safety subcommittees, which address the use of hazardous materials and radiation safety, among other issues.[74] There are approximately 110 human use subcommittees in medical facilities throughout the VA system.[75]

Most VA hospitals are affiliated with a teaching hospital or university medical center, and the IRB of the affiliated medical center may also review human subjects research conducted in VA facilities, if the VA facility does not have a human use subcommittee or if the research is a collaboration between the two institutions. Forty VA facilities use a university IRB to review human subjects research, and three others share an IRB with an affiliated medical center.[76] If VA uses the IRB of an affiliated teaching institution, then at least one VA employee with scientific expertise must sit on that board in order to represent VA interests. Similarly, there are limits on the number of members of VA IRBs who may be from affiliated teaching institutions.[77]

Any research protocol involving human subjects must be reviewed and approved by the human studies subcommittee before final review and approval by the full R&D committee. After this institutional level review, those approved proposals that are requesting VA appropriated funds are submitted to the VACO R&D office for further review. Here a final merit review is conducted by one of 18 categorical merit review Boards, composed of 10 to 15 predominantly of nonfederal scientists. Research for which VA funding is sought may also be reviewed "off-station" by experts at other VA institutions before being submitted to VACO for merit review. Those research projects conducted by VA investigators and clinicians without the support of appropriated research funds, however, do not undergo centralized review for scientific merit. Approval for the conduct of these projects rests with the local institution's R&D committee.[78]

Once a research project has begun, the local R&D committee forwards annual reports to VACO, which maintains a comprehensive database on all research conducted in VA facilities, irrespective of the source of funding. In addition, the minutes of all meetings of institutional R&D committees are submitted to VACO and reviewed by staff. If there are questions or concerns about the involvement of human subjects in proposed or ongoing research that expert reviewers raise, the institutional committee is queried further.[79]

VACO does not routinely audit IRBs, but does inspect their records and procedures if there is reason for concern.[80] Inspections are prompted, for example, when expert reviewers have questions about the safety or adequacy of human subjects protections after the local IRB has approved the research, or when adverse drug reactions occur, or when patients require care for adverse outcomes in the course of a study. In the case of large cooperative studies that include several hospitals (sometimes including institutions outside the VA system), VACO conducts site visits at participating VA facilities during which consent forms are reviewed and a sample of subjects is interviewed to verify that consent procedures have been followed. Data from randomized trials are closely monitored so that any statistical differences that emerge in treatment outcomes can be quickly detected.[81]

DEPARTMENT OF ENERGY

DOE conducts and supports research involving human subjects that ranges from diagnostic and therapeutic applications in nuclear medicine to epidemiological and occupational health studies, both

within the department's own research facilities and elsewhere under grant and contract. DOE laboratories also receive funding from other federal agencies such as NIH and from private sponsors. In fiscal year 1994, DOE supported 106 projects involving human subjects, 70 at DOE laboratories and 36 at other institutions. An additional 69 projects at DOE laboratories were funded by other agencies. DOE funding of human subjects research amounted to $46 million in this period, with an additional $10 million in support of projects at DOE laboratories coming from other agencies. One project alone, the Radiation Effects Research Foundation in Japan, received $20.4 million in DOE funding in fiscal year 1994.[82]

DOE Authority for the Protection of Human Subjects

DOE has codified the Common Rule at 10 CFR Part 745. There is no DOE statutory provision for human subjects protection.

Responsibility for Human Subjects Protections Within DOE

The Office of Health and Environmental Research (OHER) within the Office of Energy Research is responsible for formulating human subjects research policies and for ensuring department-wide compliance with the Common Rule, regardless of the DOE agency or office that conducts or sponsors the research.[83] DOE sponsorship and funding of research involving human subjects is dispersed in many offices, divisions, and laboratories throughout the department.[84]

Policies and Practices in the Oversight of Human Subjects Research

All human subjects research that is financially supported by DOE is first reviewed for scientific merit by specialized external peer review committees. Proposals for research involving human subjects then undergo in-house evaluation of merit and priority for funding. All DOE-funded research involving human subjects, whether intra- or extramural, must first be reviewed and approved by an IRB with a DOE- or OPRR-issued assurance prior to receipt of funding. Work sponsored by other public or private agencies is reviewed for scientific merit by the funding organization and for the adequacy of human subjects protections by the IRB of the DOE facility in which it will be performed.[85]

The national laboratories operated by DOE account for about 90 percent of DOE's intramural human subjects research. Each laboratory has an IRB to review all research proposals involving human subjects. Two laboratories, Pacific Northwest and Los Alamos, have MPAs with DOE; most of the others have MPAs with OPRR. A few conduct only a small number of studies involving human subjects each year and must apply for a single project assurance from DOE.[86] DOE plans to renegotiate the MPAs that it awards to its own laboratories every three to five years.[87]

In February 1994, DOE charged its externally constituted Health and Environmental Research Advisory Committee (HERAC) with the task of reviewing departmental practices with respect to research involving human subjects under the Common Rule. This evaluation, conducted by a HERAC subcommittee composed of physicians, ethicists, and research scientists, addressed policies and performance both at the research institution and departmental levels. The report of the subcommittee, *Protection of Human Research Subjects*, was transmitted to DOE on May 27, 1994.[88]

In the course of their evaluation, the HERAC subcommittee conducted site visits to eight DOE laboratories and research facilities.[89] This set of site visits constituted the first routine on-site audits of these institutions' IRBs and human subjects protection activities. DOE has preliminary plans to conduct similar reviews of IRB activities at all DOE research installations over a three-year period and to continue

such compliance reviews by "process improvement teams" (consisting of the person responsible for human subjects protections at DOE, a physician or research scientist, an ethicist, and a member of the field office or procurements staff) at all facilities on a three-year cycle thereafter.[90] At the present time, DOE investigates IRB activities only in response to reports of noncompliance or adverse outcomes.[91]

The HERAC subcommittee reported the following findings and made related recommendations for IRB and departmental reforms:

- A written delegation of authority from the director of the research lab or facility to the IRB, sufficient to allow the IRB to perform its duties, was frequently missing. The subcommittee recommended that IRBs have formal, documented delegation so that they can readily investigate problems and suspend or terminate approval of a protocol if such an action is contended.
- IRB membership requirements sometimes were not met. The subcommittee recommended that IRBs review their membership for adequate representativeness.
- Continuing (annual) review of ongoing research often received inappropriate emphasis, sometimes too involved and other times too superficial. The subcommittee recommended that IRBs should ensure full and substantive review of protocol renewals and document these reviews carefully.
- Consent forms often contained little or no substantive information about the nature of the research and the risks involved. The subcommittee recommended that all information conveyed in the consent process be in writing and in language understandable by subjects.
- Minutes of IRB meetings were often superficial and failed to note the items of information required by the Common Rule. Evidence of communications between IRBs and investigators about proposals under consideration was often absent. The subcommittee recommended that IRBs follow regulatory requirements on these various kinds of documentation scrupulously.
- The subcommittee recommended that DOE conduct regular audits of IRB performance in DOE facilities, including random sampling of patient records and signed consent forms, analogous to audits performed by FDA. It further recommended that the DOE research facilities be required to submit to DOE headquarters a copy of all FDA reports of IRB audits.
- The subcommittee recommended that research in DOE facilities that is supported by outside sources be reviewed by DOE for its compatibility with the department's mission. (This review would not take place as part of human subjects protection activities.)
- Finally, the subcommittee recommended that, in the case of the Lawrence Berkeley Laboratory, the relationship between the laboratory's small review panel and the IRB of the University of California at Berkeley be revised. The laboratory's panel had been screening proposals before submitting them to that IRB.[92]

DOE has accepted all of the above recommendations.[93]

NATIONAL AERONAUTICS AND SPACE ADMINISTRATION

NASA conducts ground-based and in-flight biomedical research involving human subjects related to space life. Management and oversight of human subject research within NASA lies with the Division of Life and Biomedical Sciences and Applications. Human subjects research conducted or supported by

NASA is divided roughly equally between intramural centers and extramural research institutions and universities. The three NASA field centers that in recent years have conducted research involving human subjects are the Ames Research Center, the Johnson Space Center, and the Kennedy Space Center. Johnson Space Center, as the lead human research center because of its program of manned space flights, has by far the greatest involvement with human subjects research. Kennedy Space Center stopped conducting research involving human subjects several years ago, when NASA consolidated its various research functions.[94]

NASA Authority for the Protection of Human Subjects

In 1986, NASA revised its 1972 policy governing the use of human subjects in research to conform with what was then the proposed model federal policy for the protection of research subjects (NASA Management Instruction [NMI] 7100.8A). The NMI applies to NASA headquarters and field installations and all extramural research in which NASA is involved to any degree.[95] The Common Rule is codified by NASA at 14 CFR Part 1230. The NMI is now under revision to bring it up to date with the 1991 regulation, and NASA expects to publish it by fall 1995.[96] NASA has convened an external Bioethics Task Force to review and provide recommendations on the content of the draft NMI, and to strengthen NASA's human subjects protections practices overall.[97]

Responsibility for Human Subjects Protections Within NASA

All human research conducted aboard NASA spacecraft, including pre-, in-, and post-flight studies, must be reviewed by the Johnson Space Center IRB, known as the Human Research Policy and Procedures Committee (HRPPC). Each center's IRB reviews not only the research conducted at or by that center, but also extramural human research that involves NASA participation.[98] Most extramural proposals are submitted by large research institutions that have negotiated MPAs with OPRR. These assurances cover many human research activities and are in effect for five years. Once an extramural proposal has been approved by the institution's IRB, it is sent to NASA headquarters for external peer review for scientific merit, administered by the American Institutes of Biological Sciences (AIBS), Information Dynamics, Inc. (IDI), NIH, or a similar disinterested peer group. Should the proposal deal with human space research, it must also be reviewed by the Johnson Space Center IRB. In essence, all human research proposals submitted to NASA must undergo external peer review for scientific merit; internal review by the IRB of the proposing institution; and, if destined for flight or NASA participation, IRB review of the relevant NASA field center.[99]

Policies and Practices in the Oversight of Human Subjects Research

Biomedical studies conducted in space undergo this rigorous review process because of special risks and the subjects' involvement in a mission, with an obvious tension existing between voluntary participation in human subjects research and job performance in manned space flight. The Johnson Space Center HRPPC reviews two types of protocols for a given space-based study. A "master protocol" consists of a detailed description of all aspects of the study; it is the first document submitted to the HRPPC for approval. The "training protocol" consists of a detailed description of the training activities to be conducted prior to a specific space flight, including objectives, a daily schedule of the training procedures, and equipment to be used. The HRPPC must approve both the master protocol and the training protocol at least six weeks before a training tour begins. In addition, Johnson Space Center's

HRPPC reviews all proposals for research involving human subjects to be conducted in space.[100]

NASA ethics policies of the late 1960's and early 1970s did not treat work-related evaluative procedures or tests as research, and thus did not deem human subjects protection rules to apply to such procedures. NASA's reasoning follows:

> Involving as a human subject a specially trained adult who knowingly follows a specialized calling or occupation generally recognized as hazardous, and for whom the test, experiment or evaluative procedure forms an integral part of his calling or occupational performance. For example, a test, experiment or evaluative procedure concerning air or space flight and involving a test pilot or astronaut ordinarily would fall within this exception. However, if a test pilot or astronaut is asked to serve as a human subject in an experiment requiring, for example, cardiac catheterization, the human research could not reasonably be considered as within the scope of his specialized calling or occupation.[101]

No such explicit exception for work-related procedures or interventions exists in the current NASA policy. "Minimal risk" does, however, have a contextual meaning in the definition of the currently effective NASA management instruction:

> "Minimal risk" means that the harm or discomfort anticipated in the proposed research is not greater, considering probability and magnitude, than that encountered in the daily lives of healthy individuals, including the recognized risks inherent in a chosen occupation, such as space flight and ground support.[102]

This definition is intended to recognize the inherently risky context within which astronauts participate in experiments. It is not intended to allow for increments in risk of the magnitude of the risk of space flight itself.

This definition is also used in the revised NMI now in draft form.[103] The draft NMI takes into account the special circumstances under which space flight personnel are engaged as research subjects by requiring detailed protocols well in advance of in-flight studies so that the carefully considered informed consent of the participants can be gained ahead of time. It also makes provision for flight personnel to decline to participate in a proposed study under some circumstances that will not prejudice management decisions about the subject's participation in the flight. Consistent with the requirement of the Common Rule, space flight personnel may withdraw from an experiment at any time.[104]

CENTRAL INTELLIGENCE AGENCY

CIA supports or conducts a small number of research studies involving human subjects each year.[105]

CIA Authority for the Protection of Human Subjects

Executive Order 12333, § 2.10, issued December 4, 1981, directs CIA to follow DHHS guidelines in the conduct or sponsorship of any research involving human subjects. CIA Headquarters

Regulation 7-1a (6) (c) further specifies that the requirements for approval of human subjects research by CIA's Human Subject Research Panel (HSRP) are those codified at 45 CFR Part 46, the DHHS codification of the Common Rule plus subparts B, C, and D, which provide additional protections to special populations.[106]

Responsibility for Human Subjects Protections Within CIA

The director of central intelligence must personally approve all research involving human subjects.[107] HSRP is responsible for reviewing and certifying to the director that the research proposal is in conformance with the DHHS rules. For extramural research, HSRP acts as an oversight body for the local IRB. For intramural research, HSRP acts as the IRB for CIA. Currently, HSRP is composed of CIA employees only: the chair is a senior physician with the Office of Medical Services, and other members are representatives from the Directorates of Operations, Intelligence, and Science and Technology. A nonvoting representative of the Office of the General Counsel must attend all HSRP meetings to provide legal advice. According to the CIA regulation, HSRP may include outside experts and consultants.[108]

Policies and Practices in the Oversight of Human Subjects Research

Proposals for research may originate with any operational unit but are usually coordinated by the Office of Research and Development. A submission to HSRP consists of a description of the research proposal, a statement of work, a letter of assurance from an IRB that the research proposed is in compliance with the institution's policy and with federal and state laws (if the proposed research is extramural), and a copy of the consent form. HSRP meets to review the proposal and the consent form. The agency officer coordinating the research application attends the meeting, describes the proposal, and provides information on the purpose, mechanics, and risks and benefits of the study. This officer conveys HSRP questions, comments and recommendations to the researcher proposing to conduct the study. HSRP must unanimously agree that the informed consent process for a project is completely adequate in order to approve the project.[109]

The CIA contracting technical representative (not necessarily the person who serves as liaison between HSRP and the investigator during the initial proposal review) is responsible for monitoring the progress of the research. This representative is responsible for reporting any adverse effects of the research to the Office of Medical Services and the Office of General Counsel.[110] CIA reports that all CIA-funded research since HSRP was formed in 1982 has conformed to the requirements of the DHHS regulations.[111] Furthermore, the Office of Inspector General (OIG) inspections staff recently conducted an investigation of CIA human subjects research conducted between 1988 and 1993 and determined that all such research was conducted in adherence to federal regulations.[112]

HUMAN SUBJECTS RESEARCH AND PROTECTION AT TEN ADDITIONAL DEPARTMENTS AND AGENCIES

The Advisory Committee requested information from ten additional federal departments and agencies that sponsor and/or conduct research involving human subjects and that are subject to the Common Rule. Table 1 displays summary information:

- department-specific statutes governing human subjects research;
- estimates of current spending on such research;

- how the department is involved in human subjects research (which subagencies, intra- or extramurally);
- resources devoted to human subjects protection activities;
- research oversight and compliance practices;
- involvement in classified research;[113] and
- the existence of additional provisions for the protection of special populations.

TABLE 1. HUMAN SUBJECTS RESEARCH & PROTECTION ACTIVITIES IN TEN DEPARTMENTS & AGENCIES

	Specific statutory authority for human subjects protection	*Annual spending on human subjects research*	*Locus of human subjects research sponsored by agency*	*Staff resources devoted to human subjects protection activities**	*Nature of research oversight and compliance activities*	*Conduct of classified research*	*Additional provisions for special populations*
Department of Agriculture	None	$46 million	Intramural and extramural	1 FTE	Agriculture Research Services, Human Studies Review Committee acts as in-house IRB and oversees extramural IRBs; also relies on OPRR MPAs	No classified research	Agency policy refers to subparts B, C, and D
U.S. Agency for International Development	None	$19.5 million	Extramural research only, some conducted overseas	0.5 - 1.0 FTE	No in-house IRB; overseas grantees may make assurances directly to AID	No classified human subjects research	Agency policy refers to subparts B, C and D of 45 CFR 46.
Department of Commerce	None	<$100,000 (for National Inst. of Standards and Technology)	Intramural and extramural	< 0.1 FTE	Prior and annual review by in-house IRB for both intra- and extramural research	No classified human subjects research	None
Consumer Product Safety Commission	None	$200,000 in FY 1995	Intramural and extramural	< 0.1 FTE	Intramural IRB also reviews extramural contract studies initially and annually	No classified human subjects research	None
Department of Education	20 USC 1232h (Protection of Pupil Rights)	Research and development spending in FY 1994: $172.4 million (no breakdown of allocation for human subjects is available)	Extramural research only	Less than 1.0 FTE	No internal IRB; contract and grant managers review proposals for compliance	No classified human subjects research	None.
Environmental Protection Agency	None (EPA requires and reviews in vitro and animal research under Toxic Substances Control Act &Federal Insect -icide, Fungicide & Pest -icide Act.)	$15 to $20 million	Intramural and extramural, some conducted overseas	2.0 to 3.0 FTEs	Intramural research reviewed by IRB at University of North Carolina under memorandum of understanding; also relies on OPRR MPAs	No classified human subjects research	Agency policy refers to subparts B, C and D of 45 CFR 46.

	Specific statutory authority for human subjects protection	*Annual spending on human subjects research*	*Locus of human subjects research sponsored by agency*	*Staff resources devoted to human subjects protection activities**	*Nature of research oversight and compliance activities*	*Conduct of classified research*	*Additional provisions for special populations*
Department of Housing and Urban Development	None	N/A	N/A	N/A	N/A	N/A	N/A
Department of Justice (Bureau of Prisons)	28 USC 509 - 510, 18 USC 4001(b) and 4042	$400,000 in FY 94	Largely intramural	0.5 FTE	Local review boards (may or may not be IRB) monitor research; research program reviews once every 2 years at prisons	No classified human subjects research	Prisons regulation 28 CFR 512; also Subpart C of 45 CFR 46.
National Science Foundation	None	$14 to $18 million	Extramural only, some conducted overseas	< 0.1 FTE	No in-house IRB; grantee institutions responsible for oversight	No classified human subjects research	None
Department of Transportation	None		Intramural and extramural		For intramural research, uses an IRB under contract; contracting officer's technical representatives monitor compliance; also relies on OPRR MPAs	No classified human subjects research	None. (FAA instructions direct IRBs to include members with special expertise if special populations are included.)

* These estimates include staff resources devoted to policy development and guidance, negotiating assurances, oversight and auditing. They exclude the time of agency staff spent as IRB members or staff, and the minimal efforts of grant and contracts personnel who track IRB approval status on research applications. Full-time equivalent (FTE) effort may represent the cumulative efforts of several persons who spend part of their time on oversight of human subjects experiments.

ENDNOTES

1. "Federal Policy for the Protection of Human Subjects; Notices and Rules," *Fed. Reg.* 28,002-28,032 (June 18, 1991). Each department and agency subject to the Common Rule codified its provisions within the agency's own regulations.

2. Lily O. Engstrom, Assistant Director, Office of Extramural Research, NIH, to Wilhelmine Miller, ACHRE, 21 February 1995 (Response to ACHRE Request 013095-E). The figure for the funding of human subjects research provided by NIH/DHHS represents the total amount of funds obligated for projects in which there was any human subjects involvement, regardless of how minimal such involvement may be. Therefore, this figure includes a share of funds that do not support human studies.

3. Federal Food, Drug, and Cosmetic Act, §505(i), 507(d) (1963) and §520(g) (1976), codified at 21 USC 355(i), 357(d), and 360(g).

4. FDA differs from the Common Rule policy most significantly in the following respects: (1) FDA does not allow for the substitution of local procedures for informed consent in research conducted abroad (the Common Rule permits this, subject to several constraints), and (2) FDA does not allow IRBs to approve waivers of the required elements of informed consent (the Common Rule does allow for certain waivers, subject to several stringent conditions). FDA *intramural* and FDA-*sponsored* research is, however, subject to the provisions of the DHHS regulation, in addition to those of the FDA regulation. In some cases, then, intra- and extramural research is subject to two sets of regulatory provisions.

5. 45 CFR § 46.204(1995)

6. Ibid. The last EAB was chartered in 1979 and disbanded in 1980. See U.S. Congress, Office of Technology Assessment, *Biomedical Ethics in U.S. Public Policy* (Washington: GPO, 1993), 11-12.

7. 45 CFR § 46.206.

8. 45 CFR § 46.207(b) and § 46.208(b).

9. 45 CFR § 46.209.

10. 45 CFR § 46.205.

11. 45 CFR § 46.211.

12. 45 CFR § 46.305.

13. 45 CFR § 46.306

14. 45 CFR § 46.304.

15. 45 CFR § 46.404. The IRB determines whether the children are of such age, maturity, and psychological state as to be capable of providing assent.

16. 45 CFR § 46.405 and § 46.406.

17. 45 CFR § 46.407.

18. Gary Ellis, Director, OPRR, to OPRR staff, 7 December 1993 ("Compliance Oversight Procedures"), and Gary Ellis in oral communication to Wilhelmine Miller, ACHRE, 30 November 1994.

19. "Federal Policy for the Protection of Human Subjects," *Fed. Reg.* 28002-28004 (June 18, 1991).

20. Kathy Hudson, Office of the Assistant Secretary for Health, to Wilhelmine Miller, ACHRE, 13 February 1995 ("Personnel Devoted to Human Subjects Protection, Public Health Service, February 1995") and Kathy Hudson to Wilhelmine Miller, 17 January 1995 ("Review of DHHS Human Subjects Protection Paper"), page 4 of marked-up draft.

21. National Institutes of Health, Office for Protection from Research Risks, *Protecting Human Research Subjects* (Washington: GPO, 1993), 2-17.

22. 45 CFR § 46.103.

23. D.A. Henderson, M.D., M.P.H., Deputy Assistant Secretary for Health for Science, to Hon. John Glenn, Chairman, Committee on Governmental Affairs, U.S. Senate, 11 May 1994 ("I am writing in response to. . ."), 8.

24. Kathy Hudson, Ph.D., Office of the Assistant Secretary for Health, DHHS, to Wilhelmine Miller, ACHRE, 19 December 1994 (ACHRE Request 120594), 2.

25. NIH Policy Manual 4017, "Review of Applications and Award of Grants Involving Human Subjects" (5 August 1994), 12-24.

26. Ibid., 8-11, 21.

27. Gary Ellis, Director, OPRR, to OPRR staff, 7 December 1993 ("Compliance Oversight Procedures").

28. D.A. Henderson to the Hon. John Glenn, 11 May 1994, op. cit., 6.

29. Kathy Hudson, Ph.D., Office of the Assistant Secretary for Health, to Donald Weightman, ACHRE, 23 February 1995 ("ACHRE Request 020995-D), 2.

30. Federal Policy for the Protection of Human Subjects, §__.109. (The provisions of the Common Rule are designated as "§ ___.000." The "___" indicates that these sections are codified within the regulations of various departments. Thus § ___.107 of the Common Rule is codified for HHS at 45 CFR § 46.107.)

31. *OPRR Reports,* "Subject: Continuing Review -- Institutional and Institutional Review Board Responsibility," no. 95-01, January 10, 1995 (ACHRE No. DHHS-011795-A).

32. Kathy Hudson, Office of the Assistant Secretary for Health, to Wilhelmine Miller, ACHRE, 17 January 1995 ("Review of DHHS Human Subjects Protection Paper"), 7 of marked-up draft.

33. Gary Ellis to OPRR Staff, 7 December 1993, op. cit., 4

34. Kathy Hudson to Wilhelmine Miller, 17 January, 1995, op. cit.

35. Ibid., 1-4.

36. It should be noted here that 45 CFR §46.116(d) permits an IRB to waive the requirement for informed consent if, among other things, the IRB finds that the research involves no more than minimal risk to the subjects.

37. Kathy Hudson, Ph.D., to Wilhelmine Miller, ACHRE, 19 December 1994, op.cit., 3. Prior to the Common Rule, DHHS issued a waiver from the provision of subpart B of the DHHS regulation (45 CFR 46) that prohibits research of greater than minimal risk on fetuses in order to approve a research project involving fetoscopy, a procedure promising substantial benefits. See *Report of the Human Fetal Tissue Transplantation Research Panel*, vol. 2, testimony of Dr. Ezra Davidson, December 1988, D83-85.

38. *Protecting Human Research Subjects,* op.cit., 2.28-2.29.

39. Ibid., 2-19

40. Sections 505(i), 507(d) and 520(g) of the Act, codified at 21 USC 355(i), 357(d) and 360(g).

41. See endnote 4 of this chapter.

42. *Protecting Human Research Subjects,* op.cit., 2-20

43. Kathy Hudson to Wilhelmine Miller, 17 January 1995, op. cit., 2.

44. Federal Policy for the Protection of Human Subjects (1991), 28,026.

45. Kathy Hudson, Ph.D., to Wilhelmine Miller, 19 December 1994, op.cit., 2.

46. Kathy Hudson, Ph.D., to Wilhelmine Miller, 17 January 1995, op.cit., 2

47. FDA Compliance Program Guidance Manual, 13 February 1994, Transmittal 94-22, Attachment A, 3-4 (ACHRE No. DHHS-122694-A).

48. Institutional Review Boards, 21 CFR § 56.105 (1995).

49. FDA Information Sheet, "Waiver of IRB Requirements," February 1989.

50. Institutional Review Boards, 21 CFR § 56.121(d) (1995).

51. 21 CFR § 56.120-121.

52. Richard V. Aghababian, M.D., President, American College of Emergency Physicians, "Statement Before the FDA/NIH Public Forum on Informed Consent in Clinical Research Conducted in Emergency Circumstances" (9 January 1995), 1-5.

53. Protection of Human Subjects (21 CFR § 50.23) (1995).

54. Federal Policy for the Protection of Human Subjects, §___.116(d) and *Protecting Human Research Subjects, op.cit.,* 2-15.

55. DOD response to ACHRE Request No. 112994-A, DRE 1.950103.001b, 10 January 1995 (ACHRE No. DOD-011095-A) and John M. Bachkosky, Office of the Director of Defense, Defense Research and Engineering, DOD, to Principal Deputy Assistant to the Secretary of Defense (Atomic Energy), 22 August 1994 ("Human Subjects Protection - Request from the White House Advisory Committee Staff").

56. 10 USC 980.

57. Protection of Human Subjects, 45 CFR §46.

58. John M. Bachkosky to Principal Deputy Assistant to the Secretary of Defense (Atomic Energy), op.cit., A-1.

59. Joseph V. Osterman, Office of the Director of Defense Research and Engineering, to Principal Deputy, Assistant to the Secretary of Defense (Atomic Energy), 27 February 1995 ("White House Advisory Committee on Human Radiation Experiments").

60. John M. Bachkosky to Principal Deputy Assistant to the Secretary of Defense (Atomic Energy), op.cit., A-1

61. Ibid., A-1, and Captain Jemionek, MSC, USN, to Ms. Miller, ACHRE, 10 January 1995 ("Listing of Principal Laboratories. . .").

62. John M. Bachkosky to Principal Deputy Assistant to the Secretary of Defense (Atomic Energy), op.cit., A-1.

63. Joseph V. Osterman to Principal Deputy Assistant to the Secretary of Defense (Atomic Energy), op.cit., 1.

64. John M. Bachkosky to Principal Deputy Assistant to the Secretary of Defense (Atomic Energy), op.cit., A-1.

65. DOD Response to ACHRE Request No. 112994-A, op.cit., A-10.

66. Protection of Human Subjects in DOD-Supported Research, DOD Directive 3216.2 (7 January 1983).

67. FDA and DOD, Memorandum of Understanding of May 1987 ("Concerning Investigational Use of Drugs, Antibiotics, Biologics, and Medical Devices by the Department of Defense").

68. Richard Pell, Jr., Deputy Chief of Staff, VA, to Jeffrey Kahn, ACHRE, 23 February 1995, ("As promised in my letter. . .").

69. Dennis B. Smith, M.D., as CMD for Research and Development to Chief of Staff, VA, 5 August 1994 ("Human Radiation Experiment," attachment M) (ACHRE No. VA-080994-B).

70. Richard Pell, Jr., to Jeffrey Kahn, ACHRE, op.cit., and Richard Pell, Jr., to Wilhelmine Miller, ACHRE, 19 January 1995 ("In response to your request. . ."), enclosure pages 9-10.

71. Veterans Benefits, 38 USC § 7331 and § 7334 (1994).

72. Dennis B. Smith, M.D., as CMD for Research and Development to Chief of Staff, VA, op. cit.

73. James L. Bernat, "The Veterans Affairs National Center for Clinical Ethics," *Kennedy Institute of Ethics Journal* 2 (1993): 385-388.

74. Dennis B. Smith, M.D., to Chief of Staff, VA, op. cit.

75. Richard Pell, Jr., Deputy Chief of Staff, to Wilhelmine Miller, ACHRE, 1 February 1995, ("The enclosed list of information. . .").

76. Ibid.

77. VA Manual, M-3, Part 1, Chapter 9, "Requirements For the Protection of Human Subjects" (30 October 1992), 9-2--9-4.

78. Dennis B. Smith, M.D., as CMD for Research and Development to Chief of Staff, VA, op. cit., and Richard Pell, Jr., to Wilhelmine Miller, ACHRE, op. cit., enclosure page 10.

79. Dennis Roth, Office of Research and Development, VA, oral communication to Wilhelmine Miller, ACHRE, 6 December 1994.

80. *Ibid.*

81. *Ibid.*

82. DOE Database, Fiscal Year 1994, reported by David Saumweber, ACHRE, to Advisory Staff, ACHRE, 17 October 1994 ("DOE Current Research") and oral communication by Susan Rose, Office of Health and Environmental Research, Office of Energy Research, DOE, to Wilhelmine Miller, ACHRE, 13 January 1995.

83. Susan L. Rose, Ph.D., Radon Manager, Health Effects and Life Sciences, Research Division, Office of Health and Environmental Research, Office of Energy Research, DOE, to Kathy Taylor, ACHRE, 31 August 1994 ("This is in response to questions. . .").

84. *Ibid.*

85. *Ibid.*

86. Office of Health and Environmental Research, DOE, *Protecting Human Subjects,* vol. 2, issue 1, (Spring 1994), 4, 8-9.

87. Susan Rose, Office of Energy Research, DOE, to Wilhelmine Miller, ACHRE, oral communication, 22 December 1994.

88. Subcommittee of the Health and Environmental Research Advisory Committee, DOE, *Review of the Office of Health and Environmental Research Program: Protection of Human Research Subjects,* May 1994.

89. *Ibid.*

90. Office of Health and Environmental Research, Office of Energy Research, DOE, *Progress Report: Protecting Human Research Subjects,* November 1994, A2.

91. Susan L. Rose, Ph.D., Health Effects and Life Sciences Research Division, Office of Health and Environmental Research, Office of Energy Research, DOE, to Wilhelmine Miller, ACHRE, 13 December 1994, ("Enclosed are my responses. . .").

92. Subcommittee of the Health and Environmental Research Advisory Committee, DOE, op.cit., 13-15.

93. Office of Health and Environmental Research, Office of Energy Research, DOE, op.cit..

94. Janis H. Stoklosa, Ph.D., NASA, to Donald Weightman, ACHRE, 7 November 1994 ("With reference to the Advisory Committee. . .").

95. Protection of Human Research Subjects, NMI 7100.8A, effective. date Nov. 18, 1986.

96. DRAFT: Protection of Human Research Subjects, NMI 7100.8B.

97. The NASA Bioethics Task Force consists of six members representing professional expertise in medical and behavioral research, bioethics, and health policy. Sara Chandros, ACHRE, to Jeff Kahn, ACHRE, 2 August 1994 (NASA Ethics Task Force Notes).

98. Human Research Policy and Procedures for Space Flight and Related Investigations, JSC-20483, Revision A, NASA, LBJ Space Center, February 1993, 1.

99. Janis H. Stoklosa to Donald Weightman, op. cit.

100. Human Research Policy and Procedure for Space Flight and Related Investigations, op. cit., 3-4

101. Human Research Policy and Procedures, NMI 7100.8, 2 February 1972.

102. Protection of Human Research Subjects, NMI 7100.8A, 18 November 1986.

103. DRAFT: Protection of Human Research Subjects, NMI 7100.8B, op. cit., 2.

104. Ibid., 9-10.

105. Inspector General's Staff, CIA, meeting with Gary Stern, ACHRE, notes from meeting of 7 March 1994.

106. CIA Headquarters Regulation 7-1a (6)(c), revised 23 December 1987, 8.

107. Inspector General's Staff, CIA, to Gary Stern, op. cit.

108. L. W. Magnuson, M.D., Chairman, Human Research Panel, CIA, to Gary Stern, ACHRE, 5 January 1995, (Questions - Advisory Committee on Human Radiation Experiments).

109. Ibid.

110. Ibid.

111. Ibid., 5.

112. Central Intelligence Agency Inspector General Report of Investigation: Agency Human Subject Research, April 26, 1995), 1.

113. As of the date of this report, we were unable to obtain complete information on original classification authority from the Departments of Agriculture, Commerce; Education; Housing and Urban Development; and the Consumer Product Safety Commission.

4

RESEARCH PROPOSAL REVIEW PROJECT

The purpose of the Research Proposal Review Project (RPRP) was to evaluate the extent to which the rights and interests of current subjects of research conducted or supported by the federal government appeared to be adequately protected, and to compare the subject protections provided afforded participants in radiation research with those in non-radiation research. In order to perform its review, the Advisory Committee collected grant applications and other relevant information (such as IRB applications) from five federal agencies and 47 grantee institutions. These proposals were categorized according to the use of ionizing radiation, biomedical category, type of disease studied, federal agency, and funding type (intramural or extramural).

Proposal materials were reviewed by a subset of Committee members and staff, including persons with technical radiation risk expertise, medical expertise, and knowledge of the appropriate standards for informed consent and selection of human subjects. The proposal materials were evaluated in order to determine whether risks and benefits, informed consent procedures, and the selection of subjects appeared to be appropriate. In addition, reviewers analyzed the documentation provided in order to discern whether research proposals and other materials available to IRBs provided sufficient information to make judgements about the protection of human subjects.

The findings and conclusions of the RPRP are summarized in chapter 15 of the final report. This chapter provides more detailed information on one aspect of the RPRP--an exploration of whether there was any apparent relationship between biomedical categories, medical condition studied, or type of funding (intramural or extramural) and the extent to which the documents suggested the interests of human subjects were being protected. Reviewers' overall impressions of the extent to which these interests appeared to be protected were summarized on a 1 to 5 scale, where 1 was taken to indicate no ethical concerns and 5 was taken to indicate serious ethical concerns.

Biomedical Categories

The documents reviewed by the Advisory Committee came from four kinds of research projects: diagnostic studies; therapeutic studies; tracer or biodistribution studies; and epidemiological or opportunistic studies. As expected, a higher proportion of studies whose documents raised concerns were found among therapeutic studies, almost all of which (41 out of 43) were rated as involving more than minimal risk.

Proposals whose documents received ratings of 4 or 5 were found among all biomedical categories except for those classified as epidemiological or opportunistic. Most of the concerns, however, were found in tracer/biodistribution and therapeutic categories. Of the 28 tracer/biodistribution studies, 4 had documents that received ratings of 4 or 5, while 8 received ratings of 3. Of the 44 therapeutic studies, 11 received a rating of 4 or 5, and 6 received a rating of 3. That a higher proportion of studies in these categories had documents that received ratings of 4 or 5 may be attributed to the fact that all but two of these studies exposed subjects to more than minimal risks. Figure 1 shows the breakdown of overall ratings for each biomedical category.

Medical Condition Studied

Studies were also classified into one of three main categories of medical research: "cancer," "cardiology," and "neither cancer nor cardiology." Reviewers found, however, that 31 percent (20/64) of the proposals in the "neither" category were actually examples of neuroscience research. As shown in Figure 2, the 17 proposals whose documents received overall ratings of 4 or 5 came primarily from the categories of cancer and neuroscience research. Both the cancer and the neuroscience studies were more likely than studies in cardiology or other areas of research to appear to place subjects at greater than minimal risk.

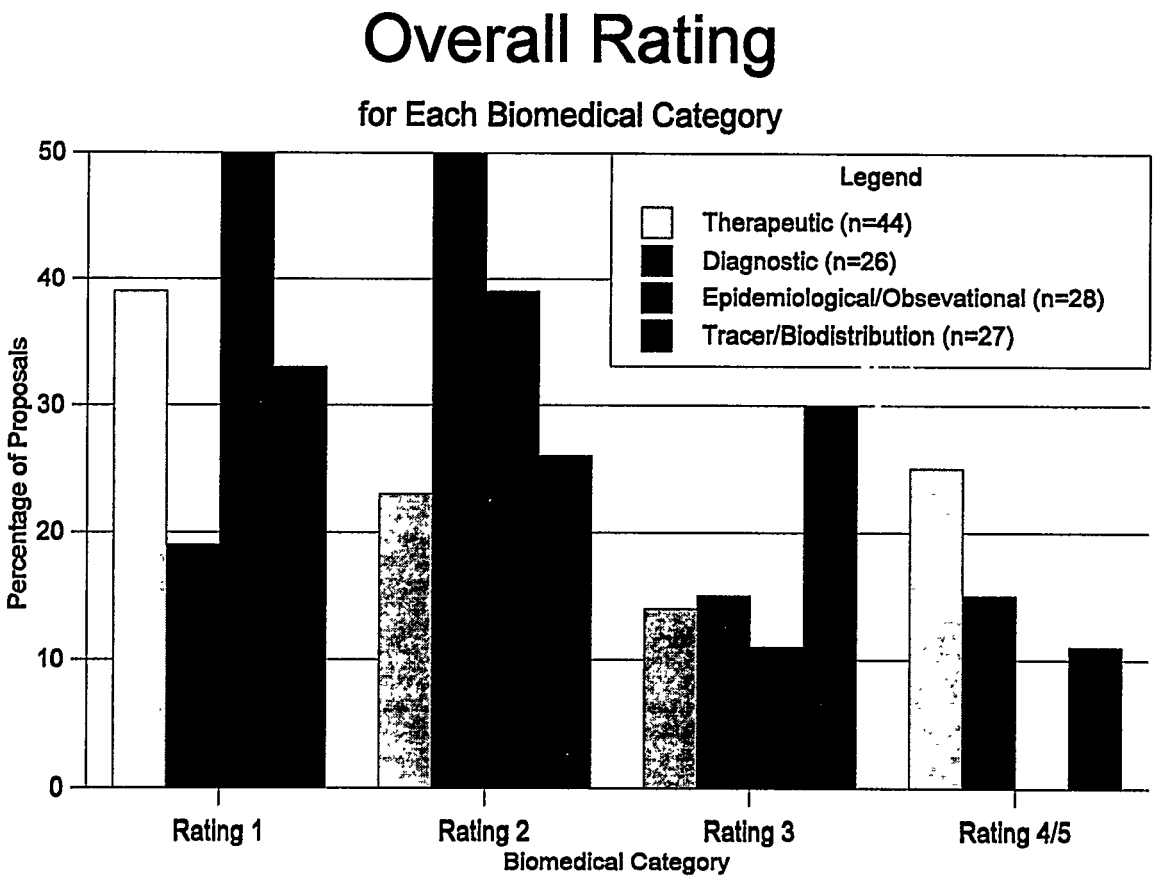
Cancer research was disproportionately represented (13/18) in proposals whose documents received overall scores of 4 or 5, as compared with their representation in the overall sample (45/125). Notably, almost all of the cancer projects we reviewed (43/45) involved greater than minimal risk. Of the 43 cancer studies involving greater than minimal risk, 13 received ratings of 4 or 5, while 6 received ratings of 3.

Twenty of the proposals in the total sample were considered neuroscience studies. From this group, 4 studies received a rating of 4 or 5, and 4 studies received a 3; all 8 of these studies involved greater than minimal risk.

Funding Type (Intramural vs. Extramural)

As shown in figure 3, of the 78 intramural projects reviewed in the total sample, 12 received ratings of 4 or 5, and 16 were rated as 3. Of the 47 extramural projects reviewed, 6 received ratings of 4 or 5, and 6 were rated as 3. The proportion of greater than minimal risk studies was identical in both extramural and intramural proposals.

Figure 1


Overall Rating
for Each Biomedical Category
Legend
Therapeutic (n=44)
Diagnostic (n=26)
Epidemiological/Obsevational (n=28)
Tracer/Biodistribution (n=27)
Percentage of Proposals
50
40
30
20
10
0
Rating 1
Rating 2
Rating 3
Rating 4/5
Biomedical Category

Supplemental Volume I

Figure 2

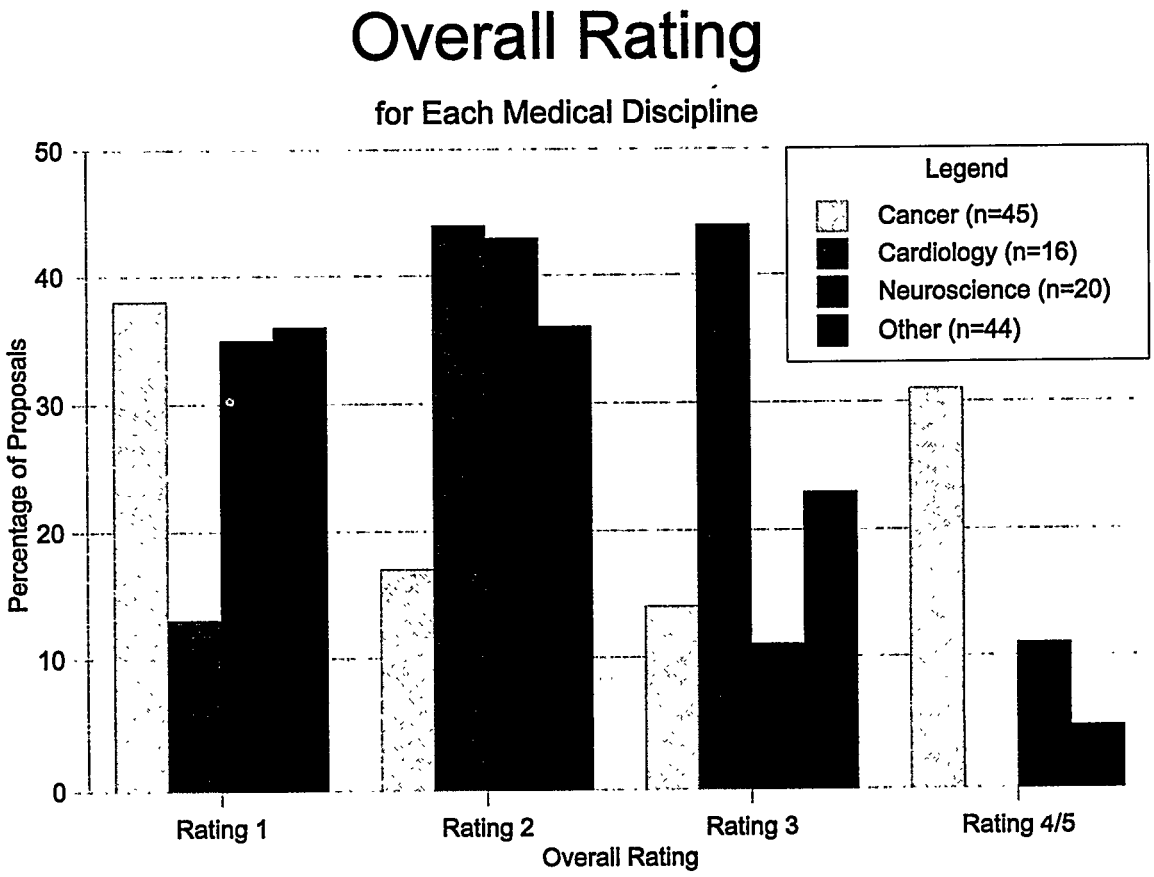


Figure 3

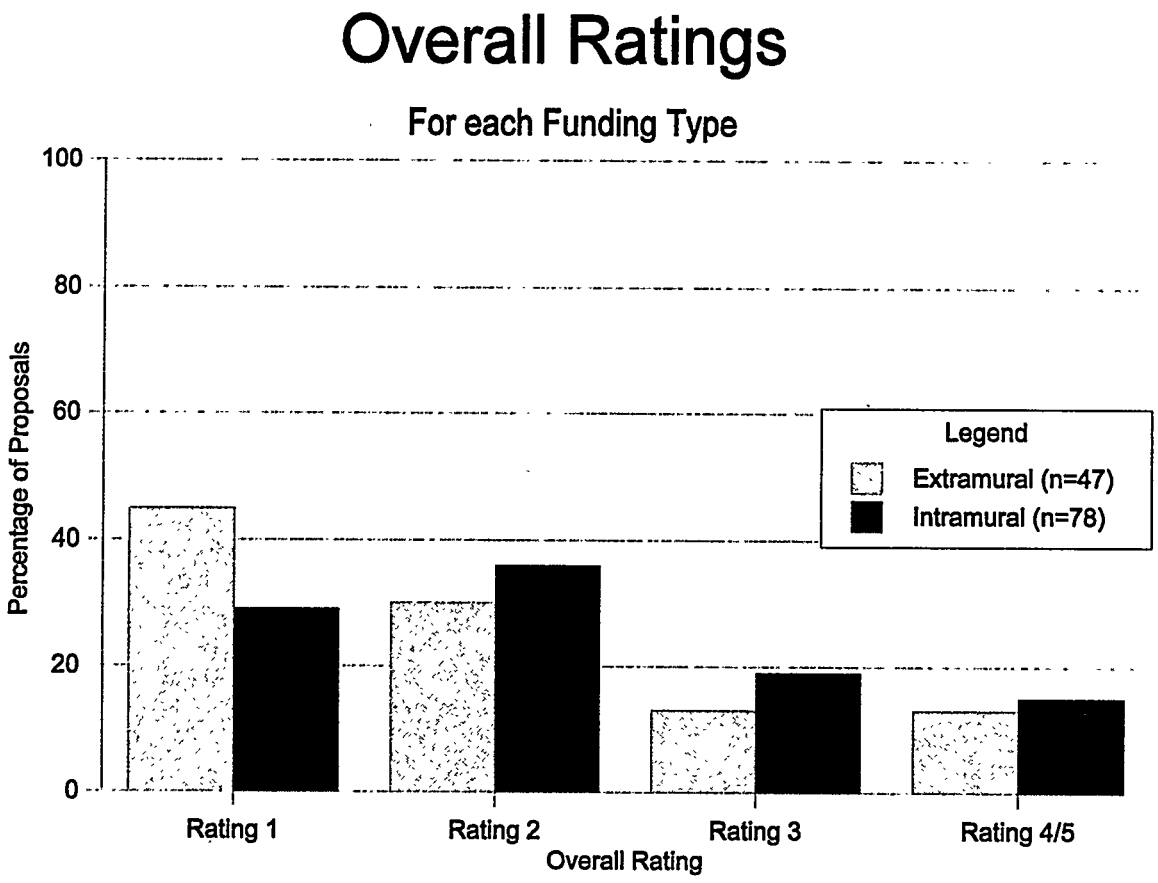

Overall Ratings
For each Funding Type
Percentage of Proposals
100
80
60
40
20
0
Legend
Extramural (n=47)
Intramural (n=78)
Rating 1
Rating 2
Rating 3
Rating 4/5
Overall Rating

Exhibit A--RPRP Proposal Review Form

Advisory Committee on Human Radiation Experiments
Research Proposal Review Project

PROPOSAL REVIEW FORM

ACHRE Protocol No. Reviewer No.
Date sent: Date completed:

Please answer each question with an "X" in the appropriate box.

I EVALUATION OF RESEARCH DOCUMENTS

1. Which research documents are included in this review?
   - ☐ Full Proposal
   - ☐ IRB Application
   - ☐ RDRC Application
   - ☐ Other

2. How adequately is each of the following topics discussed?

   a. Purpose of the Study
   - ☐ Adequately
   - ☐ Partially
   - ☐ Inadequately
   - ☐ N/A

   b. Procedures for Eligibility Screening
   - ☐ Adequately
   - ☐ Partially
   - ☐ Inadequately
   - ☐ N/A

   c. Randomization
   - ☐ Adequately
   - ☐ Partially
   - ☐ Inadequately
   - ☐ N/A

   d. Experimental Procedures (e.g., only those parts of the protocol that are experimental)
   - ☐ Adequately
   - ☐ Partially
   - ☐ Inadequately
   - ☐ N/A

   e. Potential Benefits to Subjects
   - ☐ Adequately
   - ☐ Partially
   - ☐ Inadequately
   - ☐ N/A

   f. Potential Contribution to Science
   - ☐ Adequately
   - ☐ Partially
   - ☐ Inadequately
   - ☐ N/A

   g. Risks and Burdens
   - ☐ Adequately
   - ☐ Partially
   - ☐ Inadequately
   - ☐ N/A

   h. Balance of Risks to Potential Benefits
   - ☐ Adequately
   - ☐ Partially
   - ☐ Inadequately
   - ☐ N/A

   i. Alternatives to Participation (including the choice not to participate or to withdraw)
   - ☐ Adequately
   - ☐ Partially
   - ☐ Inadequately
   - ☐ N/A

   j. Confidentiality
   - ☐ Adequately
   - ☐ Partially
   - ☐ Inadequately
   - ☐ N/A

   k. Voluntariness of Participation
   - ☐ Adequately
   - ☐ Partially
   - ☐ Inadequately
   - ☐ N/A

l. Recruitment Process
- Adequately
- Partially
- Inadequately
- N/A

Comments:

3. How adequately do the documents describe:

a. Who will solicit informed consent
- Adequately
- Partially
- Inadequately
- N/A

b. When informed consent will be solicited
- Adequately
- Partially
- Inadequately
- N/A

c. Exactly how consent will be solicited
- Adequately
- Partially
- Inadequately
- N/A

Comments:

4. Who are the proposed subjects?

Are any of the following groups included or excluded from participation in this study?

a. Adult Women
- Yes--Included
- Yes--Excluded
- Not Specified

b. Adult Men
- Yes--Included
- Yes--Excluded
- Not Specified

c. Pregnant Women
- Yes--Included
- Yes--Excluded
- Not Specified

d. Children (< = 18) ☐ Yes--Included ☐ Yes--Excluded ☐ Not Specified

e. Adult Persons of Questionable Competence ☐ Yes--Included ☐ Yes--Excluded ☐ Not Specified

f. Institutionalized Persons ☐ Yes--Included ☐ Yes--Excluded ☐ Not Specified

g. Elderly (> = 65) ☐ Yes--Included ☐ Yes--Excluded ☐ Not Specified

h. Prisoners ☐ Yes--Included ☐ Yes--Excluded ☐ Not Specified

i. Military Personnel ☐ Yes--Included ☐ Yes--Excluded ☐ Not Specified

j. Students ☐ Yes--Included ☐ Yes--Excluded ☐ Not Specified

k. Employees ☐ Yes--Included ☐ Yes--Excluded ☐ Not Specified

l. Hospitalized patients ☐ Yes--Included ☐ Yes--Excluded ☐ Not Specified

m. Ill but not hospitalized patients ☐ Yes--Included ☐ Yes--Excluded ☐ Not Specified

n. Healthy persons ("normals") ☐ Yes--Included ☐ Yes--Excluded ☐ Not Specified

o. Economically disadvantaged ☐ Yes--Included ☐ Yes--Excluded ☐ Not Specified

p. Racial/ethnic minority ☐ Yes--Included ☐ Yes--Excluded ☐ Not Specified

Specify minority:

q. Other ☐ Yes--Included ☐ Yes--Excluded ☐ Not Specified

If Other, specify:

Comments:

6. In studies that involve children or adults of questionable competence, how adequately do the documents describe:

a. Limitations to subject capacity (e.g., severity of illness as affecting patient understanding) ☐ Adequately ☐ Partially ☐ Inadequately ☐ N/A

b. Procedures for obtaining authorization from other parties according to current standards? ☐ Adequately ☐ Partially ☐ Inadequately ☐ N/A

Comments:

12. In the reviewer's judgment, is the study worth doing in terms of scientific merit?

Yes

No

Cannot evaluate

Comments:

13. Is there evidence that revisions were made to the methodology or research design that were approved by the IRB after the IRB's initial approval of the study?

Yes

No

Cannot tell

If yes, comment on the nature of these changes:

14. Are subjects being exposed to greater than minimal risk in this study?

☐ Yes

☐ Maybe

☐ No

Comments:

15. If the risk may be greater than minimal, is the risk offset by the potential benefit to the subject?

☐ Yes

☐ Maybe

☐ No

☐ N/A

16. In the reviewer's judgment, how adequate are the procedures for soliciting consent in terms of:

a. assuring voluntary decisions on the part of potential subjects?

Adequate

Partial

Inadequate

Cannot tell

b. assuring informed decisions on the part of potential subjects?

Adequate

Partial

Inadequate

Cannot tell

Comments:

ACHRE Protocol No. Reviewer No.

II CONSENT FORM(S) EVALUATION

17. Is there evidence that the consent form was revised (i.e., is there a difference between the consent form as submitted to the IRB and the consent form that was approved)?

- Yes--consent form was revised
- No--both consent forms are the same
- Don't know (only the approved consent form was received)

18. Is there evidence that revisions were made to the conset form *over time* that were approved by the IRB after the IRB's initial approval of the study?

- Yes
- No
- Cannot tell

If yes, comment on the nature of these changes:

19. How intelligible/appropriate is the reading level of the form for proposed subject population?

- Appropriate
- Problematic
- Inappropriate

Comments:

20. If the study involves children who are old enough to read, is an assent form included in the IRB materials?

- Yes
- No
- N/A

21. How adequately does the consent form address each of the following topics?

a. Purpose of the Study
- Adequately
- Partially
- Inadequately
- N/A

b. Procedures for Eligibility Screening
- Adequately
- Partially
- Inadequately
- N/A

c. Randomization
- Adequately
- Partially
- Inadequately
- N/A

d. Experimental Procedures
- Adequately
- Partially
- Inadequately
- N/A

e. Potential Benefits to Subjects (if there are no benefits to subjects but the consent form makes that clear, then check 'Adequately')
- Adequately
- Partially
- Inadequately
- N/A

f. Potential Contribution to Science
- Adequately
- Partially
- Inadequately
- N/A

g. Risks and Burdens
- Adequately
- Partially
- Inadequately
- N/A

h. Balance of Risks to Potential Benefits
- Adequately
- Partially
- Inadequately
- N/A

i. Alternatives to Participation
- Adequately
- Partially
- Inadequately
- N/A

j Cost to the Subject
- Adequately
- Partially
- Inadequately
- N/A

k. Confidentiality
- Adequately
- Partially
- Inadequately
- N/A

l. Voluntariness of Participation
- Adequately
- Partially
- Inadequately
- N/A

m. Recruitment Process
- Adequately
- Partially
- Inadequately
- N/A

Comments:

22. Does the consent form distinguish between the potential for direct benefits to subjects and benefits to medical science?
- Yes
- No--but it ought to
- No--because there are no direct benefits to the subjects

If yes, please describe:

23. Within the category/topic of risks and additional research burdens, how adequately is each of the following issues addressed:

a. Physical Risks of Eligibility Screening Procedures
- Adequately
- Partially
- Inadequately
- N/A

b. Physical Risks of Experimental Treatment/Procedure
- Adequately
- Partially
- Inadequately
- N/A

c. Physical Risks of Non-experimental Treatment/Procedure
- Adequately
- Partially
- Inadequately
- N/A

d. Physical Risks of Non-Treatment (i.e., Washout or Placebo)
- Adequately
- Partially
- Inadequately
- N/A

e. Physical Discomfort/Pain
- Adequately
- Partially
- Inadequately
- N/A

f. Inconveniences
- Adequately
- Partially
- Inadequately
- N/A

24. Is there any information in the research documents that ought to appear in the consent form(s) but does not?
- Yes
- No
- N/A

If yes, please describe:

25. If this study involves randomization between an experimental and a standard procedure, how adequate is the discussion of the risks of the experimental treatment/procedure(s) relative to the risks of the standard procedure (if a placebo is involved, check 'N/A')?
- Adequate
- Partial
- Inadequate
- N/A

Comments:

g. Psychosocial Risks
- Adequately
- Partially
- Inadequately
- N/A

h. Uncertainties/Ignorance About Risks
- Adequately
- Partially
- Inadequately
- N/A

Comments:

ACHRE Protocol No. Reviewer No.

III REVIEWER'S SUBJECTIVE EVALUATION

26. On a scale from 1 to 5, where 1 = Ethically Acceptable and 5 = Ethically Unacceptable, please rate the ethics of this research project as ascertainable from the documents available to you

- 1
- 2
- 3
- 4
- 5

Comments:

27. Is there anything not already mentioned about the research that raises ethical concerns?

- Yes
- No

If so, please describe:

5

SUBJECT INTERVIEW STUDY

This chapter provides supplemental materials and data relating to Part III, chapter 16 of the final report, the Subject Interview Study (SIS). The first part of the chapter provides a description of the detailed methodology of the Brief Survey and materials related to it, including the interview instrument, the generic consent form, and relevant research forms. The second part provides a description of the detailed methodology of the In-Depth Interview and materials related to it, including the interview guide instrument, the generic consent form, coding manual, and data entry manual. The third part provides a listing of individuals besides members of the Advisory Committee and staff who contributed to this project, including local investigators who served as liaisons at each institution; project consultants who reviewed drafts of the instrument and the SIS chapter; and expert panelists who helped to determine the level of risk associated with research projects in which respondents were enrolled. Exhibits at the end of the chapter reproduce the actual forms that were used in the SIS.

This study was approved by the Office of Management and Budget (Control number: 1910-0071) and by the Institutional Review Boards (IRBs) at each of the 16 institutions at which interviews were conducted and the 2 institutions at which focus groups and pilot testing were conducted.

BRIEF SURVEY

Detailed Methodology

Instrument Development and Pilot Testing

Once the Advisory Committee had identified the general areas to be covered in the SIS, staff and consultants developed a preliminary study design and sample questions for the Brief Survey. These were tested in a series of focus groups at two institutions that were not otherwise part of the SIS sample (the University of North Carolina at Chapel Hill and Georgetown University). Staff at Research Triangle Institute (RTI), a non-profit research company hired to assist with the SIS, drafted a formal survey instrument. The Advisory Committee, staff, and consultants revised the instrument, which was pilot tested at the same two institutions and further refined based on these pilot data. The Brief Survey instrument consisted predominantely of closed-ended items and was designed to take 5 to 10 minutes to complete. Exhibits A and B at the end of this chapter are reproductions of the final survey instrument in

English and Spanish.

Interviewers

Interviewers hired by RTI participated in a two-day training session during which they observed and practiced conducting interviews, received training in interview techniques[1], met with site coordinators, and reviewed methods of oversight and quality assurance. Interviewers who could not attend this session were trained by the site coordinators, who also provided updates and further training to all interviewers prior to beginning interviews.

Sample Selection

Advisory Committee staff and consultants set a target of 50 interviews for each clinic at each institution. Site coordinators visited the institution the week prior to data collection to get a sense of the number and demographic characteristics of patients who might be seen in relevant clinics over the course of a week. Site coordinators then developed a systematic method for approaching patients in a manner that reflected the demographics of each particular clinic. Interviewers were instructed in this sampling method, and a Patient Register was kept in each clinic to record all acceptances and refusals of participation in the SIS (see Exhibit C).

Clinic Procedures

Patients willing to participate in the Brief Survey completed a written informed consent process. Each institution was provided with a generic consent form that it could modify to satisfy institutional requirements. Exhibit D reproduces the language from this generic form. Following the Brief Survey, patients who reported that they were or had been research participants and who were willing to be contacted for an In-Depth Interview completed a Contact Sheet (Exhibit E). An Incentive Receipt (Exhibit F) was completed for each patient who completed the Brief Survey.

Data Collection and Processing

Detailed descriptions of data handling are provided in RTI's final work plan available with the federal records of the Advisory Committee. Briefly, each patient was assigned a unique identification number that was used on all project-related forms. Brief Surveys were recorded on multipage, no carbon required forms so that site coordinators could retain a copy until the originals were received and reviewed for completeness at RTI, at which time the copies were forwarded. Data were double-keyed and entered by RTI, which prepared initial frequencies and descriptive statistics and then forwarded the data to the Advisory Committee in electronic format for further analysis.

Quality Assurance

On-Site Observations

To ensure that SIS Brief Surveys were conducted in an appropriate and professional manner, Advisory Committee staff visited several institutions to observe the survey administration process. Staff

was trained to focus on the following:

- The clinic atmosphere;
- Clarity of the explanation of the Brief Survey to potential participants;
- Manner in which patients were recruited to participate;
- Process of obtaining informed consent;
- Privacy of the interviewing process; and
- Relationship among the RTI interviewers, the clinic staff, and the clinic patients.

Advisory Committee staff observed interviews at seven institutions in four cities:

- Ann Arbor (Ann Arbor Veterans Affairs Medical Center and St. Joseph's Hospital);
- Dallas/San Antonio (Dallas Veterans Affairs Medical Center and Wilford Hall Air Force Medical Center);
- Durham/Raleigh (Durham Veterans Affairs Medical Center); and
- Seattle/Tacoma (Madigan Army Medical Center and Swedish Hospital).

Advisory Committee staff generally found that the interviews were conducted well. In a few instances, staff were able to identify ways to improve the process, and these ideas were communicated to RTI.

Phone Surveys

Advisory Committee staff also conducted "quality control" phone calls to a random sample of patients who participated in the Brief Survey and agreed to be contacted again for the In-Depth Interview. At least 10 such patients from each geographic site were contacted by phone for a short interview (roughly 3-5 minutes long) about their experiences with the Brief Survey. The patients were asked how they were recruited to participate in the survey, how the survey was explained, how satisfied they were with this explanation, how comfortable they felt with their interviewer, whether they received $5 for participating in the survey, and whether they had any suggestions on ways to improve administration of the survey (see Exhibit G).

The results of the phone interviews were very positive. Of over 50 patients contacted, all reported that their general experience with the survey was good. After a few commented that the Brief Survey took a little longer than they expected, Advisory Committee staff asked RTI to include a more realistic time projection when explaining the Brief Survey to potential participants.

Determination and Verification of Research Participation

A research nurse on the Advisory Committee staff met with each site coordinator to develop an institution-specific method for determining whether there was any evidence that a patient who completed the Brief Survey was a research participant. The sources of data checked at institutions included medical and research records, a hospital computer, a research computer, research office records, and investigators' records. Site coordinators were trained to perform this procedure and record it on the Hospital/Clinic Records Data sheets (see Exhibit H).

It became apparent that in some cases there were discrepancies between patients' reports about being research participants and the information obtained from institutional records by trained abstractors. When these discrepancies emerged, health professionals on the Advisory Committee staff (a physician and a research nurse) visited each institution to review records in order to try to resolve these discrepancies (see Exhibit I).

Assessment of Risk

As described in chapter 16 of the final report, Advisory Committee staff requested copies of a blank consent form for each of the research projects in which patients who completed the Brief Survey were enrolled. A panel of experts was then convened to characterize each of the consent forms received using the form reproduced in Exhibit J at the end of this chapter.

Field Data Collection Response Rates

Table 1 includes the response rates for the Brief Survey according to city. That is, the number of hospitals and clinics in each city, the number of surveys actually completed, and the estimated response rates. See chapter 16 in the final report for additional explanation.

Table 1--SIS Brief Survey Interview Response Rates[2]

City	*Number of Hospitals*	*Number of Clinics*	*Number of Questionnaires*	*Response Rate (percent)*
Ann Arbor	3	9	288	97.4
Baltimore-Washington	5	14	539	99.1
Dallas-San Antonio	3	9	442	99.8
Durham-Raleigh	3	8	402	97.1
Seattle-Tacoma	2	5	211	72.6
TOTAL	**16**	**45**	**1882**	**94.7**

Description of Brief Survey Data Analysis

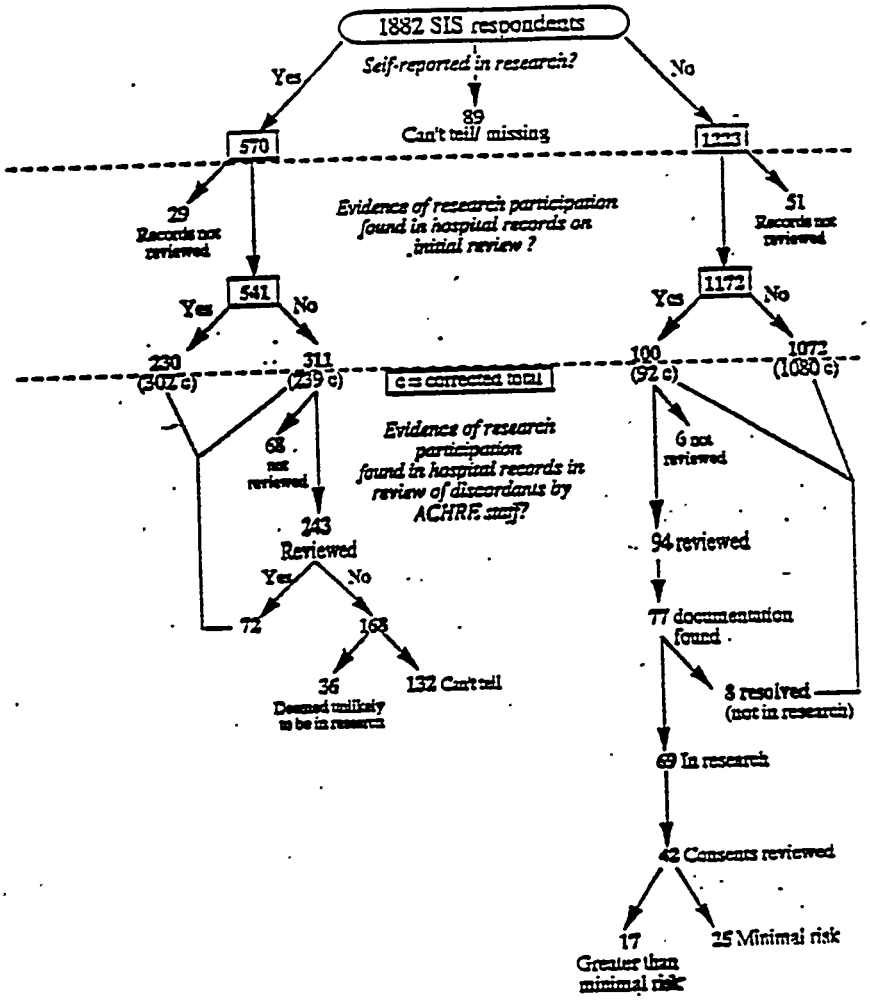
RTI double-entered the data and produced univariate and some bivariate tabulations using SAS statistical software. Advisory Committee staff ran logistic regression models using the Egret statistical software package. All further analyses were performed using JMP software (SAS Institute) on an Apple Macintosh Quadra 700 computer.

Most analyses consisted of univariate summaries or bivariate cross-tabulations. Logistic regression results are reported not as odds ratios, but as "elasticities"--that is, the absolute change in the

baseline percentages that were associated with a unit change in the reported risk factor. These were obtained by multiplying the baseline odds by a risk factor's odds ratio, and then converting all odds to absolute risks. This style of reporting was used in order to make the results interpretable to readers not familiar with logistic regression and odds ratios.

Figure 1 illustrates the numbers for each stage of the process of analyzing research participation. As part of the Brief Survey, patients were asked whether they thought they had ever been involved in medical research. RTI personnel conducted a preliminary review to find evidence of research participation. Advisory Committee staff conducted a second, more detailed review of "discordant" respondents (i.e., those where self-reported involvement and medical records differed). The corrected totals shown in the figure reflect the revision, after the Advisory Committee staff review.

Figure 1--Analysis of Discordance



IN-DEPTH INTERVIEW

Detailed Methodology

Instrument Development and Pilot Testing

The instrument used in the In-Depth Interview was a semistructured "topic guide" that addressed the four SIS domains: general beliefs and attitudes about research; personal experiences with and understanding of research; reasons for participating; and voluntariness of participation. Drawing on findings from the literature, a draft instrument guide was developed and refined, based on findings from focus groups conducted at the University of North Carolina at Chapel Hill and Georgetown University and on later pilot testing at the same institutions. Exhibit K at the end of the chapter reproduces this instrument, the In-Depth Interview Guide, in its final form.

Interviewers

Interviewers participated in a one-day training session consisting of an overview of the study domains; a review of techniques of semistructured, qualitative interviewing; a demonstration interview; an introduction to the coding process; and a review of field procedures and record keeping. As a follow-up to the training, interviewers conducted supervised, role-playing interviews. There were 13 interviewers, including one who spoke Spanish. SIS staff also provided feedback to these interviewers regarding technique and use of the interview guide based on transcripts of the initial transcripts.

Sample Selection

A sample size of 100 respondents was the target for the In-Depth Interview component of the SIS. Patients were eligible for the In-Depth Interview if (1) during the Brief Survey, they reported that they currently or formerly had been in biomedical research, and (2) if they consented to be contacted for a longer, follow-up interview. Interviewers for the Brief Survey completed a Contact Sheet for all eligible respondents, including basic demographic information, whether the respondent reported being a current vs. former research participant, and contact information (see Exhibit E).

Every effort was made to select a balanced sample of participants in terms of demographic characteristics, geographic areas, and institutions. Individuals who reported current involvement in research generally received priority for recruitment, although this preference was waived in instances in which the inclusion of a former research participant provided a better sociodemographic balance to the overall sample. At some clinics, no or few patients interviewed in the Brief Survey reported current research participation. In these instances, former research participants were designated as the candidate respondents.

Data Collection and Processing

As soon as Contact Sheets were received by site coordinators, a pool of priority candidate respondents was selected for each geographic area and institution. The interviewer assigned to each location received Contact Sheets of potential participants and scheduled six to ten interviews from the list prior to departing for his or her assignment. Interviewers arranged for the interview to occur at a place

convenient for the respondent, including clinic waiting rooms, treatment rooms, and respondents' homes. All interviews in Ann Arbor, Seattle, Dallas/San Antonio were completed over the course of a week-long visit to each of the cities. Interviews in Durham/Raleigh and Baltimore/Washington were completed by local interviewers over the entire data collection period, which spanned approximately one month.

Before the actual interview began, interviewers obtained respondents' written consent to participate. As for the Brief Survey, each institution was provided with a generic consent form which it could adopt to meet institutional requirements. The generic form is found in Exhibit L. All interviews were tape-recorded, but interviewers often also took notes to assist them in conducting a thorough interview. At the end of the interview, respondents were compensated $25 for their time. Although a Spanish-speaking interviewer was available, all respondents spoke English and all interviews were conducted in English. Upon completion of the interviews, interviewers completed an Interviewer Comments Form and an Interviewer Analysis Form noting preliminary coding and analysis issues, logistical considerations, and suggestions (see Exhibits M and N). Interviewers either express-mailed or hand-delivered completed audiotapes and forms to the central data processing location for transcription. Completed transcripts were double-spaced and formatted for coding. Tapes and transcripts were labelled only with participants' identification numbers and never with their names. Transcripts were checked for quality and completeness.

A total of 103 In-Depth Interviews were completed and recorded, representing 14 of the 16 institutions included in the SIS sample. (Because of time constraints, no interviews were conducted at the University of Michigan Medical Center and the Baltimore VA Medical Center.) The final sample eligible for analysis totalled 99 interviews. Four interviews were excluded: one audio tape was of such poor quality that it could not be transcribed, and three respondents stated clearly during the interview that they had never participated in research.

In-Depth Interview Response Rates

Table 2 presents the number of potential candidates who were actually contacted, and finally interviewed, as part of the SIS In-Depth Interview.

Table 2--SIS In-Depth Interview Response Rates

City	*Number of Candidates Contacted*	*Number of Interviews*	*Net Response Rate (percent)*
Ann Arbor	**15**	**11**	**73.3**
Baltimore-Washington	**40**	**29**	**72.5**
Dallas-San Antonio	**30**	**19**	**63.3**
Durham-Raleigh	**41**	**25**	**61.0**
Seattle-Tacoma	**19**	**19**	**100.0**
TOTAL	**145**	**103**	**71.0**

Description of In-Depth Interview Data Analysis

Interview transcripts underwent two levels of analysis: analysis of content (including the development of codes and the reading of interviews in their entirety), and analysis of the beliefs about research participation.

Interview Coding and Analysis

Based on a reading of the pilot interview transcripts, the coding team developed a preliminary set of codes--that is, themes or topic areas that recurred throughout the interviews. This set of codes subsequently was expanded to include (1) the four original analytic domains of the SIS; (2) additional topics of interest to the Advisory Committee; and (3) further issues and concepts significant to respondents themselves, as identified in the transcripts. A total of 12 broad codes comprised the final set of codes (see Exhibit O).

Of the 13 total interviewers, six also served as coders for the In-Depth Interviews (that is, highlighted and labeled portions of interview transcripts that corresponded to one of the 12 analysis codes). All coders received 1.5 days of training, including a briefing on the meaning of the individual codes, an exercise to practice coding, and an overview of the mechanics of the coding process. To ensure reliability between coders, each member of the coding team coded two transcripts individually and then met to compare their coding decisions. After training, coders received randomly assigned transcripts for coding, and selected transcripts were reviewed to evaluate coding efforts and provide further guidance to the coders.

After coding and review, coded text segments were entered in an ASCII file using TALLY qualitative analysis software and data entry was reviewed for accuracy (see Exhibit P). It was originally thought that analysis would consist of the evaluation of text segments associated with each of the 12 codes, as generated by TALLY qualitative analysis software. However, upon reading through the initial set of text excerpts, the reviewers agreed that reading transcripts in their entirety, with the 12 codes in mind, would provide a more thorough sense of the context in which remarks were made.

Review of All Transcripts

The 99 transcripts available for analysis were sorted into two groups: those whose self-reported research participation was verified by medical and research records review, and those whose self-reported participation was not verified by records review. For the latter group, respondents were considered to be "verified" or "accurate" if they (1) demonstrated reasonable knowledge of the design and purpose of a particular project; (2) identified and reasonably described research at a different institution from the one in which they were recruited for the SIS; or (3) described convincing research experiences from the distant past. A total of 90 research participants were verified, while "discordant" cases numbered 9.

Three persons comprised the analysis team, two of whom had also been interviewers. To preserve a sense of the data set as a whole, one member of the analysis team read all 99 transcribed interviews eligible for analysis. To complement this broad knowledge of the database, the person who had read all of the interviews and two other analysis team members each read and served as primary reviewer for one-third of the transcripts. Having each member of the analysis team read transcripts provided additional context for the later analysis of specific excerpts of coded text. This analysis team conferred twice to discuss its findings with respect to the 12 codes, as well as overall impressions and

potential policy implications. Their review agenda included the following questions:

- What issues and experiences were most salient to respondents?
- What was the relative frequency with which particular remarks, experiences, or beliefs occurred?
- What discrepancies or concordances did the three reviewers find in their own reading of the transcripts?
- What conclusions could be drawn about each of the 12 analysis codes (topic areas)?

ADDITIONAL AFFILIATED PROFESSIONAL INVOLVEMENT

List of Institutional Investigators

The following individuals served as local investigators at institutions selected for the SIS:

Institution	*Local Investigator*
Ann Arbor Veterans Affairs Medical Center	Roger Grekin, M.D.
Baltimore Veterans Affairs Medical Center	Sandra Marshall, M.D.
Baylor University Medical Center*	Cara East, M.D.
Clinical Center of the National Institutes of Health	Nancy Kass, Sc.D.[3]
Dallas Veterans Affairs Medical Center	Khalad Alekhteyar, M.D.
Duke University Medical Center	Eric Winer, M.D.
Durham Veterans Affairs Medical Center	Kenneth Morris, M.D.
Greater Baltimore Medical Center	Gary I. Cohen, M.D.
Madigan Army Medical Center	LTC Kenneth Bertram, M.D.
Parkland Memorial Hospital and University of Texas Southwestern Medical Center at Dallas	Eli Glatstein, M.D.
Rex Hospital	William Berry, M.D.
Seattle Veterans Affairs Medical Center*	Anthony Back, M.D.
St. Joseph's Hospital	Phillip Stella, M.D.
Swedish Hospital	Saul E. Rivkin, M.D.
The Johns Hopkins Hospital	John H. Fetting, M.D.
University of Washington Health Sciences Center*	Thomas Griffin, M.D.
University of Michigan Medical Center	Susan Dorr Goold, M.D.
Walter Reed Army Medical Center	Col Robert Mays, M.S.
Wilford Hall Air Force Medical Center	Col Ernest H. Oertli, D.V.M.

* Interviews were *not* conducted at these institutions.

Project Consultants

In designing the SIS, Advisory Committee members and staff met with specialists in medical oncology, radiation oncology, and cardiology at major research institutions across the country (Harvard University, Johns Hopkins University, Seattle VA Medical Center, University of California at San Francisco, University of Washington, and Washington University). Information from these meetings helped to identify relevant domains for investigation and shaped the structure of the SIS.

Four consultants were also engaged to comment on (1) RTI's Work Plan, (2) the survey instruments and the analytic plan, and (3) a draft of the chapter 16 of the Advisory Committee's final report. These individuals are listed below:

Bradford Gray, Ph.D.
Yale University

Charles Lidz, Ph.D.
University of Pittsburgh

Betty Levin, Ph.D.
Brooklyn College

Bernard Lo, M.D.
University of California at San Francisco

Expert Panel to Characterize Research Projects

Finally, the following individuals served as members of an expert panel to characterize the research projects that were included in the SIS sample:

Nancy L. Bartlett, M.D.
Assistant Professor of Medicine
Barnard Cancer Center
Washington University Medical Center

Peter Glassman, M.D.
Staff Physician
Dept. of General Internal Medicine
Los Angeles VA Medical Center

Perry Grigsby, M.D.
Professor of Radiation Oncology
Washington University Medical Center

Steve Larsen, M.D.
Chief of Nuclear Medicine
Memorial Sloan Kettering Hospital

Gail Povar, M.D.
Clinical Professor of Medicine and Health Care Sciences
George Washington University

Richard Stein, M.D.
Chief of Cardiology
Health Science Center
State University of New York at Brooklyn

Jeremy Sugarman, M.D., M.P.H., M.A.
Senior Policy and Research Analyst
Advisory Committee on Human Radiation Experiments

Robert K. Zeman, M.D.
Professor and Clinical Director of Diagnostic Radiology
Georgetown University Medical Center

ENDNOTES

1. A variety of materials were used in this training session conducted by RTI. See: Center for Survey Research, Field Interviewers General Manual. Research Triangle Institute, Research Triangle Park, NC: 1993.

2. Response rate calculations were based on the first 1845 questionnaires obtained.

3. Dr. Kass, a member of the Advisory Committee staff, served as principal investigator for the Clinical Center. Local support was provided by Laura Lee, R.N., as well as Greg Curt, M.D. (National Cancer Institute) and Harry Keiser, M.D. (National Heart, Lung, and Blood Institute).

EXHIBITS

Brief Survey:

- A. Instrument (English)
- B. Instrument (Spanish)
- C. Patient Register
- D. Generic Consent Form (Brief Survey)
- E. Contact Sheet
- F. Incentive Receipt
- G. Quality Assurance Interview
- H. Hospital/Clinics Records Data
- I. Analysis of Discordant Responses
- J. Characterization Data Sheet

In-Depth Interview:

- K. In-Depth Interview Guide
- L. Generic Consent Form (In-Depth Interview)
- M. Interviewer Comment Form
- N. Interviewer Analysis Form
- O. Coding Form
- P. Data-Entry Manual

EXHIBIT A

SUBJECT INTERVIEW STUDY
(Project #6106)

BRIEF SURVEY

For

The Advisory Committee on Human
Radiation Experiments (ACHRE)

By

Research Triangle Institute (RTI)
Research Triangle Park, NC 27709

Date: ____/____/95
Mon Day Yr

Time: ____:____ AM PM

ID# LABEL

Interviewer Name: _____

C1

SECTION A. ATTITUDES TOWARD MEDICAL RESEARCH

As you might recall, in this interview we are interested in your attitudes about, and experiences with, research involving human participants. By this we mean medical research done by doctors and other medical scientists in which people, not animals, are the participants or research subjects.

A1. First, I'd like to start by asking you several questions to find out your opinions about medical research involving people, conducted in the U.S. today. We are looking for your opinions. There are no right or wrong answers here ---- we're just looking for your opinion.

SHOWCARD A

A1a. If you were to describe your general attitude towards medical research involving people, would you say it is very favorable, somewhat favorable, neither favorable nor unfavorable, somewhat unfavorable, or very unfavorable?

VERY FAVORABLE 01
SOMEWHAT FAVORABLE 02
NEITHER FAVORABLE NOR UNFAVORABLE 03
SOMEWHAT UNFAVORABLE 04
VERY UNFAVORABLE 05
UNSURE/DON'T KNOW 07

SHOWCARD B

A1b. How often do you think medical research involving people helps to advance science?

NEVER 01
RARELY 02
SOMETIMES 03
USUALLY 04
ALWAYS 05
UNSURE/DON'T KNOW 07

A1c. How often do you think medical research involves unreasonable risks to people?

NEVER 01
RARELY 02
SOMETIMES 03
USUALLY 04
ALWAYS 05
UNSURE/DON'T KNOW 07

A1d. How often do you think participants in medical research are pressured into participating?

NEVER 01
RARELY 02
SOMETIMES 03
USUALLY 04
ALWAYS 05
UNSURE/DON'T KNOW 07

A1e. How often do you think patients in medical research get special treatment compared to other patients?

NEVER 01
RARELY 02
SOMETIMES 03
USUALLY 04
ALWAYS 05
UNSURE/DON'T KNOW 07

A1f. How often do you think patients who participate in medical research are better off, medically, than similar patients who are not in medical research?

NEVER 01
RARELY 02
SOMETIMES 03
USUALLY 04
ALWAYS 05
UNSURE/DON'T KNOW 07

A1g. How often do you think the doctors running medical research care more about the research than the people they study?

NEVER 01
RARELY 02
SOMETIMES 03
USUALLY 04
ALWAYS 05
UNSURE/DON'T KNOW 07

A2. Now, I'd like to ask you your beliefs about a different term. Some people think that the term clinical trial means something different from the term "medical research", while other people think they are the same. Again, I'm asking you for your opinion -- there are no "right" or "wrong" answers.

A2a. Do you think that medical research and clinical trial mean the same thing?

YES 01
[READ: "Although you think that medical research and clinical trial mean the same thing, I would still like to ask you a few questions about distinctions that some people draw between the two terms."]

NO 02
[READ: "Now I am going to ask you a series of questions asking for your opinions about medical research compared to clinical trials."]

SHOWCARD C1

A2b. Where do you think a patient is more likely to get unproven treatments or tests?

Being in medical research 01
Being in a clinical trial 02
No difference between them 03
DON'T KNOW/UNSURE 04

A2c. Where do you think a patient is more likely to be better off?

Being in medical research 01
Being in a clinical trial 02
No difference between them 03
DON'T KNOW/UNSURE 04

A2d. Where do you think a patient is likely to face greater risk?

Being in medical research 01
Being in a clinical trial 02
No difference 03
DON'T KNOW/UNSURE 04

SECTION B. RESEARCH PARTICIPATION

For the remainder of the interview we will use the term "medical research project." As we are now using it, we mean for the term "medical research project" to mean all kinds of medical research including medical experiments, clinical trials, and other health surveys.

B1. Other than this interview, are you now participating in a medical research project?

YES	01 →	SKIP TO B2
NO	02	
UNSURE	03 →	SKIP TO B2

B1a. Have you ever participated in a medical research project in the past?

YES	01 →	SKIP TO SECTION C
NO	02	

B1b. Have you ever been asked to participate in a medical research project?

YES	01	
NO	02 →	SKIP TO SECTION F

B1c. Did you decide not to participate?

YES, you decided not to participate	01 →	SKIP TO SECTION E
NO, (Explain inconsistency)	02 →	IF EXPLANATION INDICATES PRIOR RESEARCH EXPERIENCE, SKIP TO SECTION C. OTHERWISE, SKIP TO SECTION F

B2. Are you now in more than one medical research project?

YES	01 →	SKIP TO B2a
NO	02	

That means you're participating in only one medical research project, right? → SKIP TO INTRODUCTION BEFORE B3

B2a. Are any of the medical research projects you are currently participating in being done by researchers here (at this clinic/in this department)?

YES . . . . . 01 → SKIP TO B2d
NO 02

B2b. Are any of the medical research projects you are participating in being done by researchers at [INSTITUTION] but not from (this clinic or department)?

YES . . . . . 01 → SKIP TO B2e
NO 02

B2c. So you're saying that you are participating in more than one medical research project outside of [INSTITUTION], right? Which one of those projects is the most important one to you?

_____

Where does that research project take place?

_____

_____

SKIP TO INSTRUCTION BEFORE B3.

B2d. Are you participating in more than one project or experiment here (at this clinic/in this department)?

YES . . . . . 01 → SKIP TO B2f
NO 02

That means you're participating in only one medical research project here (at this clinic/in this department), right? → SKIP TO INTRODUCTION BEFORE B3

B2e. Are you participating in more than one medical research project at [INSTITUTION]?

YES . . . . . 01 → SKIP TO B2f
NO 02

That means you're participating in only one medical research project here at [INSTITUTION], right? → SKIP TO INTRODUCTION BEFORE B3

B2f. Which one of the medical research projects that you are participating in is the most important one to you?

_____

Now I'd like to ask some questions about that medical research project.

B3. To the best of your knowledge, what is the official name for this medical research project? That is, what name do you think the researchers use to describe their own project?

_____
PATIENT'S NAME FOR RESEARCH PROJECT

B4. Would you tell me briefly what (PATIENT'S NAME FOR RESEARCH PROJECT) is about?

_____

_____

_____

B5. Is the research related to a medical problem that you have?

YES, Please tell me what medical problem
that is _____ 01
NO 02

B6. Have you ever been offered the chance to participate in a medical research project and decided not to participate?

YES 01
NO 02

GO TO SECTION D

SECTION C. FORMER RESEARCH PARTICIPANTS

C1. Have you been in more than one medical research project in the past?

YES . . . . . 01 → SKIP TO C1a
NO 02

That means that you've participated in only one medical research project, right? → SKIP TO INTRODUCTION BEFORE C2

C1a. Were any of the medical research projects you participated in done by researchers here (at this clinic/in this department)?

YES . . . . . 01 → SKIP TO C1d
NO 02

C1b. Were any of the medical research projects you participated in done by researchers from [INSTITUTION] but not from (this clinic or department)?

YES . . . . . 01 → SKIP TO C1e
NO 02

C1c. So you're saying that you have participated in more than one medical research project outside of [INSTITUTION], right? Which one of those projects was the most important one to you?

_____

Where did that research project take place?

_____

_____

SKIP TO INSTRUCTION BEFORE C2

C1d. Have you been in more than one medical research project here (at this clinic/in this department)?

YES . . . . . 01 → SKIP TO C1f
NO 02

That means you've participated in only one research project here (at this clinic/in this department), right? → SKIP TO INTRODUCTION BEFORE C2

C1e. Have you been in more than one medical research project here at [INSTITUTION]?

YES 01
NO 02

That means you've particiapted in only one research project here at [INSTITUTION], right? → SKIP TO INTRODUCTION BEFORE C2

C1f. Which one of the medical research projects that you were in here, was the most important one to you?

_____

Now I'd like to ask some questions about that medical research project.

C2. To the best of your knowledge, what was the official name for this medical research project? (That is, what name do you think the researchers used to describe their own project?)

_____
PATIENT'S NAME FOR RESEARCH PROJECT

C3. Would you tell me briefly what (PATIENT'S NAME FOR RESEARCH PROJECT) was about?

_____

_____

_____

C4. Was the research related to a medical problem that you have or had at the time?

YES, Please tell me what medical problem that was _____ 01
NO 02

C5. Have you ever been offered the chance to participate in a medical research project and decided not to participate?

YES 01
NO 02

GO TO SECTION D

SECTION D. CURRENT OR FORMER RESEARCH PARTICIPANTS

D1. How long ago did you begin your participation in (PATIENT'S NAME FOR RESEARCH PROJECT)? RECORD LENGTH OF TIME AND INDICATE UNITS.

_____ YEARS 01
MONTHS 02
WEEKS 03
DAYS 04
HOURS 05

Please think about the time just before you started participating in (PATIENT'S NAME FOR PROJECT).

D2. Do you remember signing a consent form agreeing to take part in (PATIENT'S NAME FOR RESEARCH PROJECT)?

YES 01
NO 02
DON'T KNOW 03

D3. Did you think you had enough information about (PATIENT'S NAME FOR RESEARCH PROJECT) to make a good decision about whether to participate?

YES . . . . . 01 → SKIP TO D4
NO 02

IF NO, what further information would you have liked to have?

_____

_____

_____

D4. Which best describes how you came to participate in (PATIENT'S NAME FOR RESEARCH PROJECT): Did you decide on your own, did you decide with the help of others, or did other people pressure you into it?

Your own decision . . . . . 01 → SKIP TO D5
Your decision, with others helping . . . . . 02 → SKIP TO D5
You felt pressured by others into your decision. 03

D4a. Who did you feel pressured you? _____

D4b. In what way did you feel pressured?

_____

D5. Which of the following do you think the policy (is/was) for dropping out of (PATIENT'S NAME FOR RESEARCH PROJECT)? Is/Was it ...

You can drop out at any time for any reason, or 01
You can drop out only if and when doctors in charge of the project tell you that you can, or 02
Some other policy?
SPECIFY_____ 03

D6. Which of the following do you think best describes (PATIENT'S NAME FOR RESEARCH PROJECT)? Is/Was it ...

a research project studying new medical treatments (ways of treating your medical condition) 01

a research project studying new diagnostic procedures (ways of learning whether or not you have a disease or medical condition) 02

or, another kind of research project, like an interview, which does not test new medical treatments or procedures 03

DON'T KNOW 04

D7. Does this research project involve in any way the use of radiation (such as x-rays or radiotherapy)?

YES 01
NO 02
DON'T KNOW 03

D8. Did you receive any money payment from (PATIENT'S NAME FOR RESEARCH PROJECT), including payment of your medical or travel expenses?

YES 01
NO 02

D9. Please tell me in one sentence your main reason for participating in this research project:

_____

_____

_____

INTERVIEWER INSTRUCTIONS

If answer to D6 = 01 . . . . . Go To D10

If answer to D6 = 02 . . . . . Go To D21

If answer to D6 = 03 . . . . . Go To D30

If answer to D6 = DK . . . . . Go To D30
If answer to D6 = Unsure . . . . . Go To D30
If answer to D6 = NA . . . . . Go To D30

For Participants in TREATMENT RESEARCH Projects

I am going to read a list of reasons why some people choose to take part in medical research projects. For each reason, please tell me whether it contributed a lot, a little, or not at all to your participating in [PATIENT'S NAME FOR RESEARCH PROJECT].

SHOWCARD D

D10. You felt you had little choice.

CONTRIBUTED A LOT 01
CONTRIBUTED A LITTLE 02
DID NOT CONTRIBUTE 03

D11. The research project offered a chance to get better treatment.

CONTRIBUTED A LOT 01
CONTRIBUTED A LITTLE 02
DID NOT CONTRIBUTE 03

D12. The research project was a way to help others.

CONTRIBUTED A LOT 01
CONTRIBUTED A LITTLE 02
DID NOT CONTRIBUTE 03

D13. The research project was the only way to get a specific medical treatment you wanted.

CONTRIBUTED A LOT 01
CONTRIBUTED A LITTLE 02
DID NOT CONTRIBUTE 03

D14. The research project was the best way to pay for treatment.

CONTRIBUTED A LOT 01
CONTRIBUTED A LITTLE 02
DID NOT CONTRIBUTE 03

D15. Your doctor thought it would be a good idea to participate.

CONTRIBUTED A LOT 01
CONTRIBUTED A LITTLE 02
DID NOT CONTRIBUTE 03

D16. The research project sounded interesting.

CONTRIBUTED A LOT 01
CONTRIBUTED A LITTLE 02
DID NOT CONTRIBUTE 03

D17. You would get extra attention from participating in the research project.

CONTRIBUTED A LOT 01
CONTRIBUTED A LITTLE 02
DID NOT CONTRIBUTE 03

D18. The research project was a way to advance medical science.

CONTRIBUTED A LOT 01
CONTRIBUTED A LITTLE 02
DID NOT CONTRIBUTE 03

D19. Participating in the research project gave you hope.

CONTRIBUTED A LOT 01
CONTRIBUTED A LITTLE 02
DID NOT CONTRIBUTE 03

D20. You had no reason <u>not</u> to participate.

CONTRIBUTED A LOT 01
CONTRIBUTED A LITTLE 02
DID NOT CONTRIBUTE 03

GO TO SECTION F

For Participants in DIAGNOSTIC research projects

I am going to read a list of reasons why some people choose to take part in medical research or experiments. For each reason, please tell me whether it contributed a lot, a little, or not at all to your participating in [PATIENT'S NAME FOR RESEARCH PROJECT].

SHOWCARD D

D21. You felt you had little choice.

CONTRIBUTED A LOT 01
CONTRIBUTED A LITTLE 02
DID NOT CONTRIBUTE 03

D22. The research project offered a chance to get better treatment.

CONTRIBUTED A LOT 01
CONTRIBUTED A LITTLE 02
DID NOT CONTRIBUTE 03

D23. The research project was a way to help others.

CONTRIBUTED A LOT 01
CONTRIBUTED A LITTLE 02
DID NOT CONTRIBUTE 03

D24. Your doctor thought it would be a good idea to participate.

CONTRIBUTED A LOT 01
CONTRIBUTED A LITTLE 02
DID NOT CONTRIBUTE 03

D25. The research project sounded interesting.

CONTRIBUTED A LOT 01
CONTRIBUTED A LITTLE 02
DID NOT CONTRIBUTE 03

D26. You would get extra attention from participating in the research project.

CONTRIBUTED A LOT 01
CONTRIBUTED A LITTLE 02
DID NOT CONTRIBUTE 03

D27. The research project was a way to advance medical science.

CONTRIBUTED A LOT 01
CONTRIBUTED A LITTLE 02
DID NOT CONTRIBUTE 03

D28. Participating in the research project gave you hope.

CONTRIBUTED A LOT 01
CONTRIBUTED A LITTLE 02
DID NOT CONTRIBUTE 03

D29. You had no reason <u>not</u> to participate.

CONTRIBUTED A LOT 01
CONTRIBUTED A LITTLE 02
DID NOT CONTRIBUTE 03

GO TO SECTION F

For participants in EPIDEMIOLOGICAL or other research projects

I am going to read a list of reasons why some people choose to take part in medical research or experiments. For each reason, please tell me whether it contributed a lot, a little, or not at all to your participating in [PATIENT'S NAME FOR RESEARCH PROJECT].

SHOWCARD D

D30. You felt you had little choice.

CONTRIBUTED A LOT 01
CONTRIBUTED A LITTLE 02
DID NOT CONTRIBUTE 03

D31. The research project offered a chance to get better treatment.

CONTRIBUTED A LOT 01
CONTRIBUTED A LITTLE 02
DID NOT CONTRIBUTE 03

D32. The research project was the best way to pay for treatment.

CONTRIBUTED A LOT 01
CONTRIBUTED A LITTLE 02
DID NOT CONTRIBUTE 03

D33. Your doctor thought it would be a good idea to participate.

CONTRIBUTED A LOT 01
CONTRIBUTED A LITTLE 02
DID NOT CONTRIBUTE 03

D34. The research project sounded interesting.

CONTRIBUTED A LOT 01
CONTRIBUTED A LITTLE 02
DID NOT CONTRIBUTE 03

D35. You would get extra attention from participating in the research project.

CONTRIBUTED A LOT 01
CONTRIBUTED A LITTLE 02
DID NOT CONTRIBUTE 03

D36. The research project was a way to advance medical science.

CONTRIBUTED A LOT	01
CONTRIBUTED A LITTLE	02
DID NOT CONTRIBUTE	03

D37. Participating in the research project gave you hope.

CONTRIBUTED A LOT	01
CONTRIBUTED A LITTLE	02
DID NOT CONTRIBUTE	03

D38. You had no reason <u>not</u> to participate.

CONTRIBUTED A LOT	01
CONTRIBUTED A LITTLE	02
DID NOT CONTRIBUTE	03

GO TO SECTION F

SECTION E. REASONS FOR NOT PARTICIPATING

Please think about the time when you were asked to participate in a medical research project and you decided not to. (IF MORE THAN 1, THINK ABOUT THE MOST RECENT TIME.)

I am going to read a list of reasons why some people choose not to take part in medical research projects. For each reason, please tell me whether it contributed a lot, a little, or not at all to your decision not to take part in the medical research project.

SHOWCARD D

E1. Being in the medical research project would have been unpleasant.

CONTRIBUTED A LOT 01
CONTRIBUTED A LITTLE 02
DID NOT CONTRIBUTE 03

E2. The medical research project was too risky.

CONTRIBUTED A LOT 01
CONTRIBUTED A LITTLE 02
DID NOT CONTRIBUTE 03

E3. Taking part in the medical research project would have cost you money.

CONTRIBUTED A LOT 01
CONTRIBUTED A LITTLE 02
DID NOT CONTRIBUTE 03

E4. You did not want to be treated like a guinea pig.

CONTRIBUTED A LOT 01
CONTRIBUTED A LITTLE 02
DID NOT CONTRIBUTE 03

E5. Taking part in the medical research project would have been inconvenient.

CONTRIBUTED A LOT 01
CONTRIBUTED A LITTLE 02
DID NOT CONTRIBUTE 03

E6. You wanted your medical decisions to be made by your doctor and yourself, not by researchers.

CONTRIBUTED A LOT 01
CONTRIBUTED A LITTLE 02
DID NOT CONTRIBUTE 03

E7. You wanted to know what treatment you were getting.

CONTRIBUTED A LOT 01
CONTRIBUTED A LITTLE 02
DID NOT CONTRIBUTE 03

E8. Your doctor thought it was a bad idea.

CONTRIBUTED A LOT 01
CONTRIBUTED A LITTLE 02
DID NOT CONTRIBUTE 03

E9. Being in the medical research project was NOT the best way for you to get better.

CONTRIBUTED A LOT 01
CONTRIBUTED A LITTLE 02
DID NOT CONTRIBUTE 03

SECTION F. BACKGROUND INFORMATION

Now, I would like to ask just a few more general questions about your background.

F1. What is your date of birth?

_____ _____ _____
Month Day Year

F2. INTERVIEWER: IS THE RESPONDENT MALE OR FEMALE?

MALE 01
FEMALE 02

F3. Do you consider yourself to be Latino, Hispanic, or of Spanish origin or descent?

YES 01
NO 02

F4. Which of the following best describes you? Are you...

Black or African American 01
White 02
Native American or Alaskan Native 03
Asian or Pacific Islander 04
Some other race, SPECIFY _____ . . 05

F5. What is the last grade or year that you completed in school?

LESS THAN 8TH GRADE 01
SOME HIGH SCHOOL 02
HIGH SCHOOL GRADUATE OR GED 03
SOME TECHNICAL OR VOCATIONAL SCHOOL . . 04
TECHNICAL OR VOCATIONAL SCHOOL
GRADUATE 05
SOME COLLEGE 06
TWO-YEAR COLLEGE GRADUATE 07
FOUR-YEAR COLLEGE GRADUATE 08
SOME POST GRADUATE 09
POSTGRADUATE OR PROFESSIONAL DEGREE . . 10
OTHER, SPECIFY _____ 11

F6. Which of the following best describes your employment status, are you currently employed full time, part time, or are you currently not employed?

Full time 01
Part time 02
Not employed 03

SHOWCARD E

F7. Which category bes describes your combined family income, before taxes?

Greater than $75,000	01
$50,000 - $74,999	02
$25,000 - $49,999	03
Less than $25,000	04
REFUSED	05

F8. Do you think your overall health is excellent, good, fair or poor?

Excellent	01
Good	02
Fair	03
Poor	04

F9. Do you currently have medical insurance coverage of any sort?

YES	01
NO	02 → SKIP TO F10

F9a. Do you have private medical insurance (such as Blue Cross/Blue Shield) whether it is from your employer, a former employer, or on your own?

YES	01
NO	02

F9b. Do you have public medical insurance (like Medicare, Medicaid, etc.)?

YES	01
NO	02

F9c. Do you receive any VA (Veteran's Affairs) benefits?

YES	01
NO	02

F10. Is there anything else that you would like to tell us relating to the things we have been talking about in this interview

YES, SPECIFY _____

_____ . 01

NO 02

[ASK SECTION G ONLY TO THOSE WHO HAVE ANSWERED "YES" TO QUESTION B1 OR B1a.] OTHERWISE, THANK THE RESPONDENT FOR HIS/HER TIME AND END THE INTERVIEW.

SECTION G. WILLINGNESS TO PARTICIPATE IN AN IN-DEPTH INTERVIEW

We may be calling a small number of the people interviewed today for a longer interview on the same subject. This interview will be arranged for a convenient time in the next couple of weeks. The interview should last about 45 minutes and people who participate will be given $25 for their time and expenses. Would you be willing to be called by someone to set up an interview?

YES	01 →	[Interviewer complete the Contact Sheet.]
NO	02	

TIME ENDED _____:_____ AM PM

SECTION H. INTERVIEWER OBSERVATIONS (COMPLETE AFTER THE INTERVIEW)

H1. Do you think that this person was able to answer questions appropriately? e.g., do you think this person understood most of the questions?

YES 01
NO, SPECIFY_____ . . . 02

_____

H2. Was the interview conducted in a setting conducive to getting good responses?

YES 01
NO, SPECIFY_____ . . . 02

_____

[ANSWER ONLY FOR THOSE WHO ANSWERED "YES" TO QUESTION B1 OR B1a]

H3. Do you think this person would be someone who should be recruited for the in-depth interview?

YES, SPECIFY _____ . . 01

_____

NO, SPECIFY _____ . . . 02

_____

EXHIBIT B

CASO: ESTUDIO DE ENTREVISTAS
(Proyecto #6106)

ENCUESTA BREVE

Para

El Comité Asesor en Experimentos
de Radiación sobre Humanos (ACHRE)

Por

Research Triangle Institute (RTI)
Research Triangle Park, NC 27709

Fecha: ____/___/ 95
Mes Día Año

ROTULO CON #ID

Hora: _____:____ AM PM

Nombre del Encuestador: _____ **C1**

SECCIÓN A. ACTITUD HACIA LA INVESTIGACIÓN MÉDICA

Como usted recordará, en esta entrevista nos interesa observar su disposición hacia y su experiencia con investigaciones que involucran participantes humanos. Con esto queremos significar estudios médicos realizados por doctores y otros científicos de la medicina en los cuales no se usan animales sino seres humanos como objeto de la investigación.

A1. Primero, quisiera comenzar formulando algunas preguntas para conocer su opinión acerca de la investigación con seres humanos, que se realiza actualmente en los Estados Unidos. Estamos buscando su opinión. No existen aquí respuestas correctas o erróneas --- deseamos solamente su opinión.

TARJETA A

A1a. Si describiera su actitud general hacia la investigación médica incluyendo personas, usted diría que es ¿muy favorable, de algún modo favorable, ni favorable ni desfavorable, de algún modo desfavorable, o muy desfavorable?

MUY FAVORABLE	01
DE ALGÚN MODO FAVORABLE	02
NI FAVORABLE NI DESFAVORABLE	03
DE ALGÚN MODO DESFAVORABLE	04
MUY DESFAVORABLE	05
INSEGURO/NO SABE	07

TARJETA B

A1b. En su opinión, ¿con qué frecuencia la investigación médica con participantes humanos ayuda a avanzar a la ciencia?

NUNCA	01
RARAMENTE	02
ALGUNAS VECES	03
COMÚNMENTE	04
SIEMPRE	05
INSEGURO/NO SABE	07

A1c. En su opinión, ¿con qué frecuencia la investigación médica implica riesgos no razonables para las personas?

NUNCA	01
RARAMENTE	02
ALGUNAS VECES	03
COMÚNMENTE	04
SIEMPRE	05
INSEGURO/NO SABE	07

A1d. En su opinión, ¿con qué frecuencia los participantes en investigaciones médicas son presionados a participar?

NUNCA 01
RARAMENTE 02
ALGUNAS VECES 03
COMÚNMENTE 04
SIEMPRE 05
INSEGURO/NO SABE 07

A1e. En su opinión, ¿con qué frecuencia los pacientes que participan en investigaciones médicas reciben tratamientos especiales comparados con otros pacientes?

NUNCA 01
RARAMENTE 02
ALGUNAS VECES 03
COMÚNMENTE 04
SIEMPRE 05
INSEGURO/NO SABE 07

A1f. En su opinión, ¿con qué frecuencia los pacientes que participan en investigaciones médicas aventajan, médicamente, a pacientes similares que no están en investigación médica?

NUNCA 01
RARAMENTE 02
ALGUNAS VECES 03
COMÚNMENTE 04
SIEMPRE 05
INSEGURO/NO SABE 07

A1g. En su opinión, ¿con qué frecuencia a los doctores que hacen investigaciones médicas les interesa más la investigación que las personas que ellos estudian?

NUNCA 01
RARAMENTE 02
ALGUNAS VECES 03
COMÚNMENTE 04
SIEMPRE 05
INSEGURO/NO SABE 07

A2. Ahora, quisiera conocer sus ideas acerca de un término diferente. Algunas personas creen que el término prueba clínica significa algo diferente al término "investigación médica". Otras personas piensan que es lo mismo. Nuevamente, le pido su opinión -- no existen respuestas "correctas" ni "incorrectas".

A2a. Piensa usted que investigación médica y pruebas clínicas significan lo mismo?

SI 01
[LEA: "Aún cuando usted piense que investigación médica y pruebas clínicas significan la misma cosa, yo todavía quisiera hacerle unas pocas preguntas más acerca de distinciones que la gente suele hacer entre los dos términos."]

NO 02
[LEA: "Ahora voy a hacerle una serie de preguntas pidiendo su opinión en la comparación de investigación médica y pruebas clínicas."]

TARJETA C1

A2b. ¿Dónde piensa usted que un paciente tiene mayor posibilidad de ser sometido a tratamientos no probados o a pruebas?

Estando en investigación médica 01
Estando en prueba clínica 02
No hay diferencia entre ellos 03
NO SABE/NO ESTA SEGURA/O 04

A2c. ¿En qué situación piensa usted que un paciente tiene más posibilidades de mejorar?

Estando en investigación médica 01
Estando en prueba clínica 02
No hay diferencia entre ellos 03
NO SABE/NO ESTA SEGURA/O 04

A2d. ¿Cuándo piensa usted que un paciente enfrenta mayores riesgos?

Estando en investigación médica 01
Estando en prueba clínica 02
No hay diferencia entre ellos 03
NO SABE/NO ESTA SEGURA/O 04

SECCIÓN B. PARTICIPACIÓN EN INVESTIGACIÓN

En lo que resta de la entrevista usaremos el término "proyecto de investigación médica." De la forma que lo usamos, entendemos por "proyecto de investigación médica" todo tipo de investigación médica incluyendo experimentos médicos, pruebas clínicas y otras encuestas de salud.

B1. Aparte de esta entrevista, ¿está Ud participando en algún proyecto de investigación médica?

SI 01
→ SALTE A B2
NO 02
INSEGURA/O 03
→ SALTE A B2

B1a. ¿Ha participado usted alguna vez en un proyecto de investigación médica?

SI 01
→ SALTE A SECCIÓN C
NO 02

B1b. ¿Le han pedido alguna vez que participe en un proyecto de investigación médica?

SI 01
NO 02
→ SALTE A SECCIÓN F

B1c. ¿Decidió usted no participar?

SI, usted decidió no participar 01
→ SALTE A SECCIÓN E
NO, (explique la inconsistencia) 02
→ SI LA EXPLICACIÓN INDICA EXPERIENCIA PREVIA EN INVESTIGACIÓN, SALTE A LA SECCIÓN C. SI NO, SALTE A SECCIÓN F.

B2. ¿Está usted ahora participando en más de un proyecto de investigación?

SI 01
→ SALTE A B2a.
NO 02

Esto significa que usted esta participando en sólo un proyecto de investigación médica, ¿verdad?
→ SALTE A LA INTRODUCCIÓN ANTES DE B3.

B2a. ¿Algunos de los proyectos de investigación médica, en los cuales usted participa actualmente, son conducidos por investigadores de aquí (en esta clínica/ en este departamento)?

SI 01
→ SALTE A B2d
NO 02

B2b. ¿Algunos de los proyectos de investigación médica, en los cuales usted participa, son conducidos por investigadores de [INSTITUCIÓN] pero no de (esta clínica o departamento)?

SI 01
→ SALTE A B2e
NO 02

B2c. Luego, usted dice estar participando en más de un proyecto de investigación médica fuera de [INSTITUCIÓN], ¿verdad? ¿Cuál de esos proyectos es el más importante para usted?

_____

¿Dónde se lleva a cabo ese proyecto de investigación médica?

_____

_____

→ SALTE A LA INTRODUCCIÓN ANTES DE B3.

B2d. ¿Está usted participando aquí en más de un proyecto de investigación (en esta clínica/en este departamento)?

SI 01
→ SALTE A B2f.
NO 02

Esto significa que usted está participando aquí en sólo un proyecto de investigación médica (en esta clínica/en este departamento), ¿verdad?

→ SALTE A LA INTRODUCCIÓN ANTES DE B3.

B2e. ¿Está Ud. participando en más de un proyecto de investigación médica en [INSTITUCIÓN]?

SI 01
→ SALTE A B2f.
NO 02

Esto significa que Ud. está participando aquí [INSTITUCIÓN] en solo un proyecto de investigación médica, ¿verdad?
→ SALTE A LA INTRODUCCIÓN ANTES DE B3.

B2f. ¿Cuál de los proyectos de investigación médica en los cuales usted participa es el más importante para usted?

_____

Ahora quisiera hacerle algunas preguntas sobre ese proyecto de investigación médica.

B3. De lo que Ud. recuerda, ¿cuál es el nombre oficial del proyecto de investigación médica? Es decir, ¿cómo piensa usted que los investigadores le llaman a ese proyecto?

_____
NOMBRE QUE EL PACIENTE LE DA AL PROYECTO DE INVESTIGACIÓN

B4. Podría decirme brevemente de qué se trata (NOMBRE QUE EL PACIENTE LE DA AL PROYECTO DE INVESTIGACIÓN)

_____

_____

_____

B5. ¿Se relaciona la investigación con algún problema médico que Ud. tiene?

SI 01
Por favor diga cuál es el problema médico _____
NO 02

B6. ¿Le han ofrecido alguna vez la oportunidad de participar en un proyecto de investigación médica y usted decidió no participar?

SI 01
NO 02

VAYA A SECCIÓN D

SECCIÓN C. PREVIA PARTICIPACIÓN EN INVESTIGACIÓN

C1. ¿Ha estado Ud. en el pasado en más de un proyecto de investigación médica?

SI 01
→ SALTE A C1a.
NO 02

Esto significa que Ud. ha participado en el pasado en sólo un proyecto de investigación médica, ¿verdad? → SALTE A INTRODUCCIÓN ANTERIOR A C2

C1a. ¿Alguno de los proyectos de investigación médica en los que Ud. participó fue realizado por investigadores de aquí (en esta clínica/en este departamento)?

SI 01
→ SALTE A C1d.
NO 02

C1b. ¿Alguno de los proyectos de investigación médica en los que Ud. participó fue realizado por investigadores de [INSTITUCIÓN] pero no de (esta clínica o dept.)?

SI 01
→ SALTE A C1e.
NO 02

C1c. Luego, usted afirma que ha participado en más de un proyecto de investigación médica fuera de [INSTITUCIÓN], ¿verdad? ¿Cuál de esos proyectos fue el más importante para usted?

_____

¿Donde se realizó ese proyecto de investigación?

_____

_____

→ SALTE A INSTRUCCIÓN ANTERIOR A C2.

C1d. ¿Ha estado Ud. participando aquí (en esta clínica/en este departamento) en más de un proyecto de investigación médica?

SI 01
→ SALTE A C1f.
NO 02

Esto significa que Ud. ha participado aquí (en esta clínica/en este departamento) en sólo un proyecto de investigación, ¿verdad?
→ SALTE A INSTRUCCIÓN ANTERIOR A C2.

C1e. ¿Ha estado Ud. participando aquí [INSTITUCIÓN] en más de un proyecto de investigación médica?

SI 01
NO 02

Esto significa que Ud. ha participado aquí [INSTITUCIÓN] en sólo un proyecto de investigación médica, ¿verdad?
→ SALTE A INSTRUCCIÓN ANTERIOR A C2.

C1f. ¿Cuál de los proyectos de investigación médica en los cuales usted participó aquí fue el más importante para usted?

_____

Ahora quisiera hacerle algunas preguntas sobre ese proyecto de investigación médica.

C2. De lo que Ud. recuerda, ¿cuál era el nombre oficial del proyecto de investigación médica? (Es decir, ¿cómo recuerda usted que los investigadores le llamaban a ese proyecto?)

_____
NOMBRE QUE EL PACIENTE LE DA AL PROYECTO DE INVESTIGACIÓN

C3. Podría decirme brevemente de qué se trataba (NOMBRE QUE EL PACIENTE LE DA AL PROYECTO DE INVESTIGACIÓN)

_____

_____

_____

C4. ¿Se relacionaba la investigación con algún problema médico que Ud. tiene o tenía entonces?

SI 01
Por favor diga cuál era el problema médico_____
NO 02

C5. ¿Le han ofrecido alguna vez la oportunidad de participar en un proyecto de investigación médica y usted decidió no participar?

SI 01
NO 02

VAYA A SECCIÓN D.

SECCIÓN D. PARTICIPANTES EN INVESTIGACIONES PRESENTES O PASADAS

D1. ¿Hace cuánto tiempo comenzó a participar en (NOMBRE QUE EL PACIENTE LE DA AL PROYECTO)? REGISTRE EL TIEMPO E INDIQUE LAS UNIDADES.

____ AÑOS 01
MESES 02
SEMANAS 03
DÍAS 04
HORAS 05

Por favor piense precisamente en el momento anterior a comenzar a participar en (NOMBRE QUE EL PACIENTE LE DA AL PROYECTO DE INVESTIGACIÓN).

D2. ¿Recuerda Ud. haber firmado un formulario de aceptación acordando tomar parte en (NOMBRE QUE EL PACIENTE LE DA AL PROYECTO DE INVESTIGACIÓN)?

SI 01
NO 02
NO SABE 03

D3. ¿Pensó Ud. que tuvo información suficiente sobre (NOMBRE QUE EL PACIENTE LE DA AL PROYECTO) para tomar una buena decisión sobre participar o no del proyecto?

SI 01
→ SALTE A D4.
NO 02

SI NO, ¿que otra información le hubiera gustado tener?

_____

_____

_____

D4. ¿Qué afirmación describe mejor cómo decidió participar en (NOMBRE QUE EL PACIENTE LE DA AL PROYECTO): Decidió Ud. mismo, decidió Ud. con la ayuda de otros, o alguna otra persona lo presionó a participar?

Decisión propia 01
→ SALTE A D5.
Su decisión, con la ayuda de otros 02
→ SALTE A D5.
Ud. se sintió presionado por otros en su decisión 03

D4a. ¿Quién siente que lo presionó? _____

D4b. ¿De que modo se sintió presionado? _____

_____

D5. ¿Cuál de las siguientes afirmaciones es/era la norma para el abandono de (NOMBRE QUE EL PACIENTE LE DA AL PROYECTO)? usted piensa que ...

Ud. puede abandonar en cualquier momento por cualquier razón, o 01
Ud. puede abandonar sólo si y cuando el doctor a cargo del proyecto le dice que puede hacerlo, o 02
¿Alguna otra norma?
ESPECIFIQUE_____ . . 03

D6. ¿Cuál de las siguientes frases describe mejor (NOMBRE QUE EL PACIENTE LE DA AL PROYECTO)? Es/era ...

un proyecto de investigación que estudia nuevos tratamientos médicos (modos de tratar su condición médica) 01

un proyecto de investigación que estudia nuevos procedimientos de diagnóstico (modo de saber si Ud. tiene alguna enfermedad o problema crónico de salud) 02

otro tipo de proyecto de investigación, como ser una entrevista, que no prueba nuevos tratamientos o procedimientos médicos . . 03

NO SABE 04

D7. ¿Incluye este proyecto de investigación, de alguna manera, el uso de radiación (como rayos X o radioterapia)?

SI 01
NO 02
NO SABE 03

D8. ¿Recibió Ud. algún pago en dinero del (NOMBRE QUE EL PACIENTE LE DA AL PROYECTO), incluyendo el pago de gastos médicos o de viajes?

SI 01
NO 02

D9. Por favor dígame en una frase el principal motivo de su participación en este proyecto de investigación:

_____

_____

_____

INSTRUCCIONES PARA LOS ENCUESTADORES

Si la respuesta a D6 = 01 . . . . . Vaya a D10

Si la respuesta a D6 = 02 . . . . . Vaya a D21

Si la respuesta a D6 = 03 . . . . . Vaya a D30

Si la respuesta a D6 = NO SABE . . . . . Vaya á D30

Si la respuesta a D6 = NO ESTA SEGURO . . . . . Vaya a D30

Si la respuesta a D6 = NO RESPONDE . . . . . Vaya a D30

Para Participantes en Proyectos de INVESTIGACIÓN DE TRATAMIENTOS

Le voy a leer una lista de razones por las cuales algunas personas eligen participar en proyectos de investigación médica. Para cada razón, por favor dígame si ella contribuyó mucho, poco, o nada a su participación en (NOMBRE QUE EL PACIENTE LE DA AL PROYECTO).

TARJETA D

D10. Sintió que tenía pocas alternativas.

CONTRIBUYO MUCHO 01
CONTRIBUYO POCO 02
NO CONTRIBUYO 03

D11. El proyecto de investigación ofrecía la alternativa de un tratamiento mejor.

CONTRIBUYO MUCHO 01
CONTRIBUYO POCO 02
NO CONTRIBUYO 03

D12. El proyecto de investigación era una manera de ayudar al prójimo.

CONTRIBUYO MUCHO 01
CONTRIBUYO POCO 02
NO CONTRIBUYO 03

D13. El proyecto de investigación era la única manera de obtener un tratamiento específico que usted deseaba.

CONTRIBUYO MUCHO 01
CONTRIBUYO POCO 02
NO CONTRIBUYO 03

D14. El proyecto de investigación era la mejor manera de pagar por un tratamiento.

CONTRIBUYO MUCHO 01
CONTRIBUYO POCO 02
NO CONTRIBUYO 03

D15. Su médico pensó que participar sería una buena idea.

CONTRIBUYO MUCHO 01
CONTRIBUYO POCO 02
NO CONTRIBUYO 03

D16. El proyecto de investigación parecía interesante.

CONTRIBUYO MUCHO 01
CONTRIBUYO POCO 02
NO CONTRIBUYO 03

D17. Usted obtendría atención extra por participar en el proyecto de investigación.

CONTRIBUYO MUCHO 01
CONTRIBUYO POCO 02
NO CONTRIBUYO 03

D18. El proyecto de investigación era una manera de hacer avanzar la ciencia médica.

CONTRIBUYO MUCHO 01
CONTRIBUYO POCO 02
NO CONTRIBUYO 03

D19. Participar en el proyecto de investigación le dio esperanzas.

CONTRIBUYO MUCHO 01
CONTRIBUYO POCO 02
NO CONTRIBUYO 03

D20. Usted no tenía ninguna razón para no participar.

CONTRIBUYO MUCHO 01
CONTRIBUYO POCO 02
NO CONTRIBUYO 03

VAYA A SECCIÓN F

Para Participantes en Proyectos de Investigación de DIAGNÓSTICOS

Le voy a leer una lista de razones por las cuales algunas personas eligen participar en proyectos de investigación médica. Para cada razón, por favor dígame si ella contribuyó mucho, poco, o nada a su participación en (NOMBRE QUE EL PACIENTE LE DA AL PROYECTO).

TARJETA D

D21. Sintió que tenía pocas alternativas.

CONTRIBUYO MUCHO 01
CONTRIBUYO POCO 02
NO CONTRIBUYO 03

D22. El proyecto de investigación ofrecía la alternativa de un tratamiento mejor.

CONTRIBUYO MUCHO 01
CONTRIBUYO POCO 02
NO CONTRIBUYO 03

D23. El proyecto de investigación era una manera de ayudar al prójimo.

CONTRIBUYO MUCHO 01
CONTRIBUYO POCO 02
NO CONTRIBUYO 03

D24. Su médico pensó que sería una buena idea participar.

CONTRIBUYO MUCHO 01
CONTRIBUYO POCO 02
NO CONTRIBUYO 03

D25. El proyecto de investigación parecía interesante.

CONTRIBUYO MUCHO 01
CONTRIBUYO POCO 02
NO CONTRIBUYO 03

D26. Usted obtendría atención extra por participar en el proyecto de investigación.

CONTRIBUYO MUCHO 01
CONTRIBUYO POCO 02
NO CONTRIBUYO 03

D27. El proyecto de investigación era una manera de hacer avanzar la ciencia médica.

CONTRIBUYO MUCHO 01
CONTRIBUYO POCO 02
NO CONTRIBUYO 03

D28. Participar en el proyecto de investigación le dio esperanzas.

CONTRIBUYO MUCHO 01
CONTRIBUYO POCO 02
NO CONTRIBUYO 03

D29. Usted no tenía ninguna razón para no participar.

CONTRIBUYO MUCHO 01
CONTRIBUYO POCO 02
NO CONTRIBUYO 03

VAYA A SECCIÓN F

Para Participantes en EPIDEMEOLOGIA u otros Proyectos de Investigación

Le voy a leer una lista de razones por las cuales algunas personas eligen participar en proyectos de investigación médica. Para cada razón, por favor dígame si ella contribuyó mucho, poco, o nada a su participación en (NOMBRE QUE EL PACIENTE LE DA AL PROYECTO).

TARJETA D

D30. Sintió que tenía pocas alternativas.

CONTRIBUYO MUCHO 01
CONTRIBUYO POCO 02
NO CONTRIBUYO 03

D31. El proyecto de investigación ofrecía la alternativa de un tratamiento mejor.

CONTRIBUYO MUCHO 01
CONTRIBUYO POCO 02
NO CONTRIBUYO 03

D32. El proyecto de investigación era la mejor manera de pagar por el tratamiento.

CONTRIBUYO MUCHO 01
CONTRIBUYO POCO 02
NO CONTRIBUYO 03

D33. Su médico pensó que sería una buena idea participar.

CONTRIBUYO MUCHO 01
CONTRIBUYO POCO 02
NO CONTRIBUYO 03

D34. El proyecto de investigación parecía interesante.

CONTRIBUYO MUCHO 01
CONTRIBUYO POCO 02
NO CONTRIBUYO 03

D35. Usted obtendría atención extra por participar en el proyecto de investigación.

CONTRIBUYO MUCHO 01
CONTRIBUYO POCO 02
NO CONTRIBUYO 03

D36. El proyecto de investigación era una manera de hacer avanzar la ciencia médica.

CONTRIBUYO MUCHO 01
CONTRIBUYO POCO 02
NO CONTRIBUYO 03

D37. Participar en el proyecto de investigación le dio esperanzas.

CONTRIBUYO MUCHO 01
CONTRIBUYO POCO 02
NO CONTRIBUYO 03

D38. Usted no tenía ninguna razón para no participar.

CONTRIBUYO MUCHO 01
CONTRIBUYO POCO 02
NO CONTRIBUYO 03

VAYA A SECCIÓN F

SECCIÓN E. RAZONES PARA NO PARTICIPAR

Por favor piense en el momento en que se le pidió participar en el proyecto de investigación médica y decidió no hacerlo. (SI SUCEDIÓ MAS DE UNA VEZ, PIENSE EN LA MAS RECIENTE).

Le voy a leer una lista de razones por las cuales algunas personas eligen no participar en proyectos de investigación médica. Para cada razón, por favor dígame si ella contribuyó mucho, poco, o nada a su decisión de no participar en el proyecto de investigación médica.

TARJETA D

E1. Estar en el proyecto de investigación médica hubiera sido incómodo.

CONTRIBUYO MUCHO 01
CONTRIBUYO POCO 02
NO CONTRIBUYO 03

E2. El proyecto de investigación médica era muy riesgoso

CONTRIBUYO MUCHO 01
CONTRIBUYO POCO 02
NO CONTRIBUYO 03

E3. Participar en el proyecto de investigación médica le hubiera costado dinero.

CONTRIBUYO MUCHO 01
CONTRIBUYO POCO 02
NO CONTRIBUYO 03

E4. No quería ser tratado como un conejillo de indias.

CONTRIBUYO MUCHO 01
CONTRIBUYO POCO 02
NO CONTRIBUYO 03

E5. Hubiera sido inconveniente participar del proyecto de investigación médica.

CONTRIBUYO MUCHO 01
CONTRIBUYO POCO 02
NO CONTRIBUYO 03

E6. Usted deseaba que las decisiones médicas fuesen tomadas por su médico y por usted mismo, no por investigadores.

CONTRIBUYO MUCHO 01
CONTRIBUYO POCO 02
NO CONTRIBUYO 03

E7. Usted deseaba saber qué tratamiento le estaban dando.

CONTRIBUYO MUCHO 01
CONTRIBUYO POCO 02
NO CONTRIBUYO 03

E8. Su médico pensó que no era buena idea participar.

CONTRIBUYO MUCHO 01
CONTRIBUYO POCO 02
NO CONTRIBUYO 03

E9. Estar en el proyecto de investigación médica NO era la mejor manera de mejorar su salud.

CONTRIBUYO MUCHO 01
CONTRIBUYO POCO 02
NO CONTRIBUYO 03

SECCIÓN F. ANTECEDENTES

Ahora, desearía hacerle unas pocas preguntas más sobre sus antecedentes.

F1. ¿Cuál es su fecha de nacimiento?

_____ _____ _____
Mes Día Año

F2. ENCUESTADOR: ¿ES EL ENTREVISTADO MUJER O VARÓN?

VARÓN 01
MUJER 02

F3. ¿Se considera usted Latino, Hispano, o de origen o ascendencia Española?

SI 01
NO 02

F4. ¿Cuál de las siguientes alternativas lo describe mejor a Ud.? Es Ud.

Negro o Afro-Americano 01
Blanco 02
Indígena, Americano o de Alaska 03
Asiático o Isleño del Pacífico 04
Alguna otra raza, ESPECIFIQUE _____ 05

F5. ¿Cuál es el último grado o año escolar que usted completó?

MENOS DE 8VO GRADO 01
ESCUELA SECUNDARIA INCOMPLETA 02
GRADUADO DE SECUNDARIA O GED 03
ESCUELA TÉCNICA O VOCACIONAL INCOMPLETA . 04
GRADUADO DE ESCUELA TÉCNICA O VOCACIONAL 05
UNIVERSIDAD INCOMPLETA 06
GRADUADO UNIVERSITARIO DE DOS AÑOS 07
GRADUADO UNIVERSITARIO DE CUATRO AÑOS . . 08
POSTGRADO INCOMPLETO 09
POSTGRADO O TITULO PROFESIONAL 10
OTRO, ESPECIFIQUE _____ 11

F6. ¿Cuál de las siguientes alternativas describe mejor situación de empleo, está usted empleado con dedicación exclusiva, mediA dedicación, o desempleado?

Dedicación exclusiva 01
Media dedicación 02
Desempleado 03

TARJETA E

F7. ¿Cuál categoría describe mejor los ingresos combinados de su familia, sin descontar impuestos?

Más de $75,000 01
$50,000 - $74,999 02
$25,000 - $49,999 03
Menos de $25,000 04
SE NEGÓ A RESPONDER 05

F8. ¿Piensa Ud. que su salud en general es excelente, buena, regular, o pobre?

Excelente 01
Buena 02
Regular 03
Pobre 04

F9. ¿Tiene Ud. actualmente cobertura de seguro médico de algún tipo?

SI 01
NO 02
→ SALTE A F10.

F9a. ¿Tiene Ud. seguro médico privado (como Blue Cross/Blue Shield) ya sea de su empleador actual, de un empleador anterior, o por su propia cuenta?

SI 01
NO 02

F9b. ¿Tiene Ud. seguro médico público (como Medicare, Medicaid, etc.)?

SI 01
NO 02

F9c. Recibe Ud. algún beneficio de VA (Veteran Affairs/Grupo de Veteranos)?

SI 01
NO 02

F10. ¿Hay algo más que quisiera decirnos en relación a los temas que estuvimos hablando durante esta entrevista?

SI, ESPECIFIQUE _____

_____ 01
NO 02

[HAGA LAS PREGUNTAS DE LA SECCIÓN G SOLAMENTE A AQUELLOS QUE HAYAN CONTESTADO "SI" A LAS PREGUNTAS B1 O B1a.] EN CASO CONTRARIO, AGRADEZCA A EL/LA ENCUESTADO/A POR SU TIEMPO Y FINALICE LA ENTREVISTA.

SECCIÓN G. DESEOS DE PARTICIPAR EN UNA ENTREVISTA MAS A FONDO

Probablemente llamemos hoy a cierto número de las personas entrevistadas para una entrevista más larga sobre el mismo tópico. Acordaremos un horario conveniente para esta próxima entrevista dentro de las próximas dos semanas. La entrevista tendrá una duración de unos 45 minutos y los participantes recibirán $25 por su tiempo y gastos. ¿Desearía usted ser llamado para arreglar una entrevista?

SI 01
→ ENCUESTADOR COMPLETE LA HOJA DE CONTACTO
NO 02

HORA DE FINALIZACIÓN _____:_____ AM PM

SECCIÓN H. OBSERVACIONES DEL ENCUESTADOR (COMPLETE DESPUÉS DE LA ENTREVISTA)

H1. ¿Piensa usted que esta persona pudo contestar las preguntas adecuadamente? Por ejemplo, ¿piensa usted que esta persona entendió la mayoría de las preguntas?

SI 01
NO, ESPECIFIQUE _____ 02

_____

H2. ¿Se condujo la entrevista en un lugar propicio para obtener buenas respuestas?

SI 01
NO, ESPECIFIQUE _____ 02

_____

[RESPONDA SOLO PARA AQUELLOS QUE CONTESTARON "SI" A LAS PREGUNTAS B1 O B1a.]

H3. ¿Piensa que esta persona es una de las que deberían ser elegida para la entrevista en profundidad?

SI, ESPECIFIQUE _____ . 01

_____

NO, ESPECIFIQUE _____ 02

_____

SUBJECT TERVIEW STUDY
(l . ject #6106)

P ___ of ___

EXHIBIT C

BRIEF SURVEY PATIENT REGISTER (BY CLINIC)

1	2	3	4	5	6	7
Patient ID#	Name	Brief Survey Consent to Participate? YES/NO	If NO, Reason for Refusal (See Codes Below)	Can We Contact For In-depth Interview? YES/NO	If NO, Reason For Refusal (See Codes Below)	Thinks of Self as Research/Exper. Patient? YES/NO
730						

Reasons for Refusal: 01 - Not Interested, 02 - Too Ill, 03 - Not Enough Time Before/After Appt., 04 - Other, Specify _____

EXHIBIT D: GENERIC CONSENT FORM (BRIEF SURVEY)

PURPOSE OF STUDY:

The Advisory Committee on Human Radiation Experiments was established by the President of the United States earlier this year to examine the ethics of research with human subjects. Although the Committee mostly is looking at how radiation research was conducted in the past, the Committee is also interested in how radiation research and research in other areas of medicine are conducted now. Therefore, we are interested in interviewing a lot of patients, some of whom are participants in research and some of whom are not. We want to know whether patients believe they are part of a medical research study and, if they think they are, to ask them more questions about their participation in that study. We are approaching patients who are being seen in either the cardiology, medical oncology, or radiation oncology clinic here at [institution]. We are conducting similar interviews with patients at many medical centers all over the country.

PROCEDURES:

If you agree to participate, we will interview you for about 5-10 minutes. During that interview, we will ask you questions about whether or not you think you are part of a medical research study and, if so, why you chose to participate and who else helped you to make that decision. We also will ask for your permission to talk to anyone else here who also might know if you currently are in a medical research study, such as your doctor, a researcher, a research nurse, or by looking at your medical record.

In order to protect your confidentiality, all interview forms only will have an identification number on them, and never your name. The list that links your name to your identification number always will be kept separate from any sheets that have information about you on them and eventually will be destroyed.

If you decide to participate in this study, we will reimburse you $5 for your time.

We also will ask everyone who agrees to be interviewed whether they would be willing to have a longer interview at another time and place that is convenient for them. People who have this second interview will receive an additional $25.

RISKS/BENEFITS:

There are no physical or medical risks to you by participating in this study since it is only an interview study. It is possible that some of the questions we ask might make you uncomfortable or unhappy since some of them will be related to your health and your illness. However, we expect that most patients will find our questions easy to answer. Also, you do not have to answer any questions that you do not want to answer. There is no direct benefit to you by answering our questions. However, you will be helping us to learn more about what patients think about medical research. This will help us to better explain research studies to future patients.

If you decide to participate, you do not have to answer any question that makes you uncomfortable, and you can change your mind about participating at any time. You will have the same quality of medical care here whether or not you decide to be interviewed.

If you want to talk to anyone further about this research study please call Dr. Winston Liao at (919) XXX-XXXX or [Dr. ___ at this institution and local IRB telephone #].

If you agree to join this study, please sign your name below.

SUBJECT INTERVIEW STUDY
(Project #6106)

EXHIBIT E

CONTACT SHEET

ID# Label

Use this form only for those respondents who complete the Brief Survey, thought of themselves as being research or experimental patients and consented to be contacted for the In-Depth Interview. [THUS, COMPLETE ONLY FOR PATIENTS LISTED ON THE BRIEF SURVEY REGISTER WITH A "YES" IN COLUMN 7.]

PATIENT NAME MUST BE OBLITERATED PRIOR TO SHIPMENT

Name _____
First Middle Last

Street Address: _____

_____

City: _____ State: _____ Zip: _____

Telephone number: (____)_____ (____)_____
(home) (work)

What would be the best time/place to contact you _____

FROM THE BRIEF SURVEY:

1. Now a research subject (Q.B1) ——— Yes ..... 01 No 02
2. Previously a research subject (Q.B1a) ——— Yes ..... 01 No 02
3. Date of birth (Q.F1) ____/____/____
   Month Day Year
4. Sex (Q.F2) ——— Male ..... 01 Female 02
5. Spanish origin or descent (Q.F3) ——— Yes ..... 01 No 02
6. Race (Q.F4) ——— Black ..... 01 White ..... 02 All Others 06
7. Last grade of school completed (Q.F5)

8th or less 01	Some college 06
Some High School 02	2 year College graduate 07
High School graduate 03	4 year College graduate 08
Some technical/vocational 04	Some Post Graduate study 09
Technical/vocational graduate 05	Post Graduate Degree 10
Other 11	

8. Private medical insurance (Q.F9a) ——— Yes ..... 01 No ..... 02 Blank 00
9. Public medical insurance (Q.F9b) ——— Yes ..... 01 No ..... 02 Blank 00
10. Veteran's Affairs (VA) benefits (Q.F9c) Yes ..... 01 No ..... 02 Blank 00
11. Do you think this person would be someone who should be recruited for the in-depth interview? (Q.H3)

    01 .....YES (SPECIFY) _____

    02 ..... NO (SPECIFY) _____

[PLACE LABEL HERE]

EXHIBIT F

SUBJECT INTERVIEW STUDY
(Project #6106)

INCENTIVE RECEIPT

To compensate you for the time you spent answering our questions, we are paying you $5.00 cash. To indicate that you received the money, and so that the interviewer can be reimbursed, please sign below:

I received $5.00 today.

Name (Please Print) _____

Signature _____ Date: ___/___/___

Signature of Interviewer _____ Date: ___/___/___

Disposition: Original and yellow to Site Coordinator. Pink to client.

EXHIBIT G

BRIEF INTERVIEW QUALITY ASSURANCE

Hi, I'm _____ and I work with the group that interviewed you recently in the hospital waiting room about medical research. In addition to that first short interview, I know that you also agreed to talk to us again for a longer interview. I don't know if you've had that second, longer interview yet, but I just wanted to see if that first short interview was O.K. My questions for you now are not part of any interview. Instead, I just want to know how it was for you when the interviewer talked to you, whether you were treated politely, whether it went like you thought it would, and whether you have any suggestions for improving any part of our study.

Would you mind if I just asked you a few questions now? (Either way..... Thank you.)

(1) How was your general experience with the brief interview?_____

_____

_____

_____

_____

_____

_____

_____

(2) How were you asked to be in the interview?_____

_____

_____

_____

(3) How was the interview explained to you?_____

(4) Was this explanation right? That is, given what you were told, was the interview what you thought it would be like?

(5) How was the interviewer who did the survey? For instance, was the interviewer polite? Did you feel comfortable with the interviewer?

(6) Where did the interview take place?

Was this O.K.?

(7) Were you paid the $5?

(8) Those are all of my questions. Your feedback is really helpful. Is there anything else that we should know, or any way that we could do the interview better?

Once again, thanks for your participation, time, and effort. Have a nice day.

SUBJECT INTERVIEW STUDY
(Project #6106)

EXHIBIT H

HOSPITAL/CLINIC RECORDS DATA

[COMPLETE FOR ALL PATIENTS LISTED ON THE BRIEF SURVEY REGISTER WITH A "YES" IN COLUMN 3.]

1. Patient Study ID #: [ID# Label]

PATIENT NAME MUST BE OBLITERATED PRIOR TO SHIPMENT ↓

2. Patient Name: _____
First Middle/Maiden Last

3. Patient Date of Birth: ____/____/____
Mon. Day Yr.

4. Patient Hospital ID #: _____
(or Clinic ID #, Medical Record ID #, etc.)

5. Patient Medical Diagnosis: _____
(Use ICD-9-CM Code and/or a Written Description)

6. How many of the following sources did you check in your search for this patient's possible participation in a medical research project/experiment?

a.	Hospital Computer	YES 01,	NO .... 02 → If NO, why not _____	(See Codes Below)
b.	Research Computer	YES 01,	NO .... 02 → If NO, why not _____	(See Codes Below)
c.	Medical Record	YES 01,	NO .... 02 → If NO, why not _____	(See Codes Below)
d.	Research Records	YES 01,	NO .... 02 → If NO, why not _____	(See Codes Below)
e.	Research Nurse	YES 01,	NO .... 02 → If NO, why not _____	(See Codes Below)
f.	Research PI	YES 01,	NO .... 02 → If NO, why not _____	(See Codes Below)
g.	Other, Specify below	YES 01,	NO 02	

_____

Codes: 01 - Source not relevant for this institution
02 - Established that patient was/is a research participant via another source
03 - Other, Specify _____

7. Is there any evidence that this patient is currently participating in, or has ever participated in, a medical research project or medical experiment at this hospital?

YES .... 01 NO 02

8. If YES, what was the primary source of this information? _____
(Insert code from Q.6 above, a-g)

9. If YES, provide as much of the information requested below as possible. If the patient participated in more than one medical research project/experiment, provide this same information for that other project(s) on the back of this form.

9a. Project/Experiment Title: _____

Principal Investigator Name: _____

9b. Project/Experiment Abstract Available: YES .... 01 NO .... 02 IF YES, where can a copy be obtained?

_____

9c. Project/Experiment Signed Patient Consent: YES .... 01 NO .... 02 IF YES, where can a copy be obtained?

_____

C8. Patient states that research was at another institution ☐ Yes ☐ No

If yes, record supporting open-ended data element

C9. Patient's statement suggests that what he/she participated in was not actually research.

☐ Yes
☐ No

If yes, record supporting open-ended data element

C10. Patient's statement suggests that what he/she participated in was survey research only.

☐ Yes
☐ No

If yes, record supporting open-ended data element

C11. Comments

C12. Verified that the patient is/was a research subject? ☐ Yes ☐ No

If yes, has the Hospital/Clinic Records Data Sheet been updated? ☐ Yes ☐ No

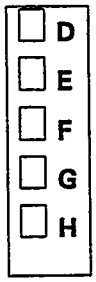
C13. Status after Review (choose one)

☐ **No longer discordant**
☐ **Remains discordant**
☐ **Unable to determine (specify below)**

If No longer discordant, choose one: ☐ A ☐ B ☐ C

A. Participation verified at institution
B. Participation at another institution verified
C. Participation at another institution suggested but not verified

If Remains discordant, choose one:



D. Unable to resolve because research would likely be at another institution
E. Unable to resolve at this institution due to unavailability of records
F. Review suggests that respondent not likely to be a research participant (specify why below)
G. Insufficient information from open-ended responses
H. For other reason (specify below)

Specify why respondent is not likely to be a research participant:
Specify other reason:

If Unable to determine, explain:

EXHIBIT I

SUBJECT INTERVIEW STUDY

ANALYSIS OF DISCORDANT RESPONSES

A1. Patient ID#

A2. Type of Discordance **(Choose one)**

- ☐ **A2(a)**
- ☐ **A2(b)**

a. Patient does not believe he/she was a research participant--but we have documentation that he/she was a participant. **[Go to B3]**

b. Patient believes he/she was was a research participant--but we have been unable to document such participaton. **[Go to C6]**

B3. Verification of Documentation

a. Verified documentation?

- ☐ **Yes**
- ☐ **No**

b. How?

B4. Date of enrollment in documented study [MM/DD/YY]

B5. Comments

B6. Status after Review:

- ☐ **No longer discordant**
- ☐ **Remains discordant**
- ☐ **Other**

(Choose one)

If Remains discordant, go to B7
If Other, comment:

B7. If Remains discordant, select all that apply:

- ☐ **Follow-up visits from prior research intervention at time of SIS interview**
- ☐ **Survey research**
- ☐ **Minor intervention (e.g. tube of blood)**

If Minor intervention, please specify:

EXHIBIT J.

CHARACTERIZATION DATA SHEET

I.D. NUMBER_____

POPULATION DISEASE BURDEN

LOW _____
MEDIUM _____
HIGH _____

RESEARCH INCREMENTAL RISK

MINIMAL _____
GREATER THAN MINIMAL _____

TYPE

TREATMENT_____
DIAGNOSTIC_____
OTHER _____

Attachment 2: In-Depth Interview Guide

INTERVIEWER NAME _____ PATIENT ID# _____

SUBJECT INTERVIEW STUDY
(PROJECT #6106)

In-Depth INTERVIEW

INTERVIEW GUIDE:
Production Version

For

The Advisory Committee on
Human Radiation Experiments (ACHRE)

By

Research Triangle Institute (RTI)
P. O. Box 12194
Research Triangle Park, NC 27709

EXHIBIT K

Ask these questions as written

☐ Key points to cover

- Possible questions for use when respondent doesn't spontaneously provide key information.

- Important concepts are printed in **bold**

If the respondent cannot recall which of several research project was of interest in Brief Survey interview, use the following priorities.

PRIORITIES FOR PROJECT SELECTION

1. Project conducted by researcher at CLINIC where interview conducted
2. Other project at INSTITUTION where interview conducted
3. Project from anywhere outside INSTITUTION where interview conducted

Tiebreaker: Project that is most important to respondent

BEGINNING THE INTERVIEW

- Thank you for coming. I'm glad you were able to make time to talk with me today (particularly considering your illness).

- We really appreciate your help; you are the expert. We know a lot about conducting research, but not enough about what it's like to be in it! We need to learn from people like you so we can do your job better.

- I am _____. (*Be neutral, non-threatening, familiar*)

  YOU MAY WANT TO SAY SOMETHING PERSONAL ABOUT YOURSELF, SUCH AS WHY THIS TOPIC IS IMPORTANT TO YOU.

- The purpose of this interview is to find out your experiences, opinions, and ideas about participating in medical research. These interviews are being conducted as part of a national study for a Presidential Advisory Committee. The information we collect will assist the Committee to develop polices and procedures for medical research. We need your assistance to ensure that policy recommendations are workable, successful, and make good sense to patients like you.

- The entire session will be tape recorded, but your responses will not be linked to you personally. So feel free to say whatever is on your mind.

- There are no right or wrong answers.

- We want to hear what you think; about your beliefs, opinions, and ideas.

- We also want to know where your opinions differ from others you know and others we have already spoken to. So don't worry if you think you what you have to say is "a little different."

- The discussion should take about 45 minutes.

- Do you have any questions for me? Okay, let's begin.

A. DESCRIPTION OF RESEARCH

When you were interviewed a few (minutes/days/weeks) ago, I understand that you told the interviewer that you were (once) involved in a research project. I would like to ask a few more questions about that.

A1. Please tell me about that research project.

744

What does (did) it involve? What do (did) you have to do?

☐ **What do you call this type of research?**

- **What's your name for this project?**
- **What kind of research study is it?**

SUBJECT INTERVIEW STUDY: In-depth Interview Guide *PRODUCTION VERSION*

☐ **Does (Did) it involve anything that's new or special or different from regular medical treatment?**

- **special drugs or treatments?**
- **medical exams or tests?**
- **questionnaires or other information collected?**

☐ **In your opinion, why is this research project being done?**

- **Who will benefit from the results of this research? Other participants? Others later on? The researchers? How?**
- **How do you think the information from the research project will be used?**
- **Is that why you're participating in the research project?**
- **What's in it for you?**

A. DESCRIPTION OF RESEARCH (continued)

☐ Are there other patients in this research project?

A2. *{T}* **Are all patients in this research project getting identical (medical) procedures or doing the same things?**

- *{T}* What other treatments are people in the research project getting? (*Look for possibility of assignment to placebo/control group*)
- *{T}* How is it decided who gets which treatment?

  (*Look for awareness of possibility of random assignment vs. Therapeutic Misconception [I'll get what's best for me]*)
- *{T}* How would/do you feel about the possibility of testing a new treatment but not getting it?

☐ Do you know any (or have you gotten to know any) of the other participants in this research project?

☐ Did they have the same experience as you have?

☐ How were they different?

B. MEDICAL CONDITION

B1. Is the research project related in some way to a medical (problem or) condition that you have?

IF YES:

Please tell me about that medical condition.

When was it first diagnosed? When did you find out that you had...?

Who told you that you had...? Was it someone at this hospital?

☐ How serious do you consider this medical condition?

☐ **Do you have medical insurance pays/paid for your treatment in general (for things not related to this research study)? {Is it Private (like Blue Cross or an HMO)? Public (like Medicare)? VA Benefits?}**

☐ *{I}* **What do they usually do to treat people with this condition?**

- **As a research participant, is your treatment different? How?**
- **Do many others with this condition participate in research?**

☐ *{I}* **Why are you in a research study rather than just getting that standard treatment?**

- *{I}* **Were there any other ways to deal with your condition (other than this research project)?**
- **What were those alternatives?**

IF NO:

☐ **Was there something else about you that made the researchers want you in their research project?**

☐ **Why are you participating in a research project that's unrelated to your current medical condition?**

C. INTRODUCTION TO PROJECT

C1. What did you know about the project before you decided to participate?

- ☐ Who told you about the research project?
- ☐ What kinds of questions did you have? How were they answered?
- ☐ What did he/she/they tell you about the research project?
  - What benefits were described? (Benefits of treatment? Benefits of participating in research?)
  - Were you told about any financial benefits? (Money payments or coverage of medical expenses)?
  - What risks or side-effects were described? (Risks of treatment? Risks of participating in research?)

SUBJECT INTERVIEW STUDY: In-depth Interview Guide *PRODUCTION VERSION*

- ☐ What did they tell you about getting out of the research project? About changing your treatment in the middle?

Think back to when you first heard about this research project.

- ☐ What was going on at that time?
  - How would you describe your medical condition at that time? Were you in the hospital then?
  - Do you feel like you made a good decision about participating in the research project?
- ☐ How did you first hear about this research project?
  - Who told you about it?
  - Where were you when you learned about it?
  - How did you find out that you could be involved?
- ☐ How was the research project explained to you?

D. DECISION TO PARTICIPATE

D1. After you heard about the research project, how did you become involved?

- ☐ Did you talk with anyone about whether or not you should take part? Who?
  - What did this person say?
  - Did you think this person wanted you to participate? Why?
  - Anyone else?
- ☐ Who made the decision to participate?
  - What made you decide to participate?
  - What went through your mind as you thought about taking part in the research project?

D2. Did you feel any pressure to take part, either from family, doctors, or from someone else? Please tell me about that.

- ☐ What did they say or do that made you feel pressured?

  Did you feel uneasy about the decision?
- ☐ Did you feel you could say no? Why or why not?
- ☐ What kinds of choices did you have had you decided not to take part in the research project?
- ☐ How long after you first heard about the research project did it take for you to decide to take part?

  Did you have any reasons not to participate?

E. EXPERIENCES AFTER DECIDING TO PARTICIPATE

E1. After you had decided to take part in the research project, what did you do to become a part of it?

Was there any sort of formal enrollment into the project?

☐ Do you remember signing anything to show that you agreed to take part in the research project? What kinds of things did it cover?

Who was there when you signed the papers?

☐ Was anything done to help you pay for treatment or services because you were going to take part in the research project? Tell me more about that.

E2. Now that you're in (While you were in) the project, do (did) you feel like you could withdraw if you wanted to? At any time?

SUBJECT INTERVIEW STUDY: In-depth Interview Guide *PRODUCTION VERSION*

☐ Did you feel pressured to stay in the research project?

Do you think the pressure to stay in is different from pressure to first participate?

☐ Did you ever want to get out of the research? Why?

Why didn't you withdraw?

E. EXPERIENCES AFTER DECIDING TO PARTICIPATE (continued)

E3. Since you have been involved in the research project, have you been satisfied or dissatisfied? Why?

- ☐ What do/did you like, or what is good, about the research project? What do/did you dislike or what was bad, about the research project?
  - Has being in a research project been a good experience? A bad experience?
- ☐ *(T)* What kind of side effects or problems does (did) participation in the research project cause?

  Was this problem caused by the treatment itself or by the fact that you are/were in a research project?
- ☐ *(T)* What good experiences does (did) participation in the project give you?

  - Was this benefit due to the treatment itself or by the fact that you are/were in a research project?
- ☐ What do you think that you will get (have gotten) out of being involved in this research project?
- ☐ How do you think it would have been for you if you had decided not to take part in the research project? For example, the care you have received, the costs, and the time that it requires.

  How do you feel about these differences? How do you deal with...?

E4. Would you participate again in a research project? Why?

  Under what circumstances?

- ☐ If a friend had the same condition as you, would you recommend that your friend take part?
  - What would you say were the best things about this research project?
  - The most difficult things?

F. EXPERIENCE IN OTHER RESEARCH PROJECTS

F1. Have you ever taken part in any other medical research project?

- Please tell me about that.
- Was it (also) related to a medical condition you have?

How did that project compare to this project?

F2. Have you ever been asked to take part in another medical research project and decided not to participate?

- Please tell me about that.
- Why did you participate in this research project and not that one?

G. MEANING OF RESEARCH-RELATED TERMINOLOGY

Sometimes people use different words or phrases to describe medical research.

G1. What does the term "medical research" mean to you?

- In your own words, how would you define "medical research?"

☐ Here are some other terms sometimes used in talking about research (*SHOW CARD*):

- Study
- Clinical trial
- Medical experiment
- Clinical investigation

G2. In your opinion, what, if anything, is different about the kinds of research that these terms refer to?

☐ What kind of research is the project we've been discussing today?

- What term would you use to describe this research project?

- Would you use one of these terms to describe the research project we've been discussing? Which one? Why?

- Would you use some other term to describe the research project?

If your doctor said that there was one study of each of these types that might help your condition, which one would you be most interested in? Why?

- Which one would you least want to participate in? Why?

SUBJECT INTERVIEW STUDY: In-depth Interview Guide *PRODUCTION VERSION*

CONCLUDING THE INTERVIEW

▸ Thank you. You've answered all my questions. Is there anything else you would like to add? Anything at all?

FINAL ACTIVITIES

- CLARIFY ANY POTENTIAL MISUNDERSTANDINGS OR QUESTIONS
- A "FAKE" ENDING OR TURNING OFF THE RECORDER SOMETIMES PROMPTS PEOPLE TO SAY WHAT IS "REALLY" ON THEIR MINDS.

IF THIS OCCURS, TAKE NOTES

- PROVIDE A CONTACT ADDRESS OR TELEPHONE NUMBER IF REQUESTED OR APPROPRITATE, SO THAT PARTICIPANTS MAY REACH YOU IF THEY HEAR OR THINK OF ANYTHING ELSE THAT MIGHT BE RELEVANT.
- ENGAGE THE LINGERERS IN DISCUSSION

STUDY
CLINICAL TRIAL
MEDICAL EXPERIMENT

When you were interviewed a few (minutes/days/weeks ago, I understand that you told the interviewer that you were (once) involved in a research project. I would like to ask a few more questions about that.

SECTION	Content of Question (key concept)	Page	NOTES
DESCRIPTION OF RESEARCH	A1. Please tell me about that research project.	1	
	A2. Are all patients in this research project getting identical (medical) procedures or doing the same things?	2	
MEDICAL CONDITION	B1. Is the research project related in some way to a medical (problem or) condition that you have?	3	
INTRODUCTION TO PROJECT	C1. What did you know about the project before you decided to participate?	4	
DECISION TO PARTICIPATE	D1. After you heard about the research project, how did you become involved?	5	
	D2. Did you feel any pressure to take part, either from family, doctors, or from someone else? Please tell me about that.	5	
	D3. What were your reasons for participating in the research project?	5	
EXPERIENCES AFTER DECISION TO PARTICIPATE	E1. After you had decided to take part in the research project, what did you do to become a part of it?	6	
	E2. Now that you're in (While you were in the project), do (did) you feel like you could withdraw if you wanted to? At any time?	6	
	E3. Since you have been involved in the research project, have you been satisfied or dissatisfied? Why?	7	

	I4. Would you participate again in a research project? Why?	7	
OTHER RESEARCH EXPERIENCE	F1. Have you ever taken part in any other medical research project?	8	
MEANING OF RESEARCH	G1. What does the term "medical research" mean to you?	9	
RELATED TERMINOLOGY	G2. In your opinion, what, if anything, is different about the kinds of research that these terms refer to? (SHOW CARD	9	

EXHIBIT L: GENERIC CONSENT FORM (IN-DEPTH INTERVIEW)

PURPOSE OF STUDY:

We would like to gather more detailed information concerning your participation in medical research. We are asking everyone who already has completed a short interview who said they are participants in medical research if they are willing to be interviewed for a longer period -- about 45 minutes -- about the same topics as we discussed with you when you completed the short interview.

PROCEDURES:

If you agree to participate, we will interview you for about 45 minutes. This interview will be audiotaped. During the interview, we will ask you questions about why you chose to join a medical research study and who else helped you to make that decision. We will ask you what you think are the advantages and disadvantages of participating in medical research.

In order to protect your confidentiality, the audiotape only will have an identification number on it, and not your name. The list that links your name to your identification number always will be kept separate from any sheets or tapes that have information about you on them and eventually will be destroyed.

Everyone who completes this second interview will be paid $25 at the time the interview is conducted to partially reimburse you for your time and to offset any costs you might have incurred related to the study, such as travel or parking.

RISKS/BENEFITS:

There are no physical or medical risks to you by participating in this study since it is only an interview study. It is possible that some of the questions we ask might make you uncomfortable or unhappy since some of them will be related to your health and your illness. However, we expect that most patients will find our questions easy to answer. Also, you do not have to answer any questions that you do not want to answer. There is no direct benefit to you by answering our questions. However, you will be helping us to learn more about what patients think about medical research. This will help us to better design and explain research studies to future patients.

If you decide to participate, you do not have to answer any question that makes you uncomfortable, and you can change your mind about participating at any time. You will have the same quality of medical care here whether or not you decide to be interviewed.

If you want to talk to anyone further about this research study please call Dr. Winston Liao at (919) XXX-XXXX or [Dr. ___ at this institution and local IRB telephone #].

If you agree to join this study, please sign your name below.

EXHIBIT M

Interviewer's Comments
In-Depth Interviews
Subject Interview Study
Advisory Committee on

Issues for Interviewers		
Name of Interviewer:		Today's Date:
Interviewer I.D.	Time Began:	Time Ended:
Place:		
Recruitment Strategy:		

1. Describe any logistical difficulties that need to be addressed in future interviews.

2. How would you describe the personality/characteristics of this respondent?

3. What major themes, opinions, norms, or ideas came out of this In-Depth interview?

4. Any new ideas that came up? Anything that might require a new analysis code?

5. What issues should be followed up in future In-Depth interviews?

6. Were there any questions that worked particularly well?

   Were there any questions that didn't work at all?

7. Were there any problems with this interview that should be taken into account in the analysis?

8. Was this a good In-Depth interview? Why?

EXHIBIT N

Interviewer Analysis Form
In-Depth Interviews
Subject Interview Study
Advisory Committee on

DO NOT WRITE HERE

1. What was the respondents general attitude toward research? 1. ___

   ☐ Positive

   ☐ Negative

2. How sure was the respondent that he/she was a research participant? 2. ___

   ☐ Very Sure

   ☐ Somewhat Sure

   ☐ Not At All Sure

3. Did the respondent consider there to be any risks to research participation? 3. ___

   ☐Yes

   ☐No

4. Did the respondent feel he/she **chose** whether or not to participate? 4. ___

   ☐Yes

   ☐No

5. Did the respondent report any pressures to participate **not related to illness?** 5. ___

☐ None

☐ Some

☐ A lot

6. Did the respondents' description of study disclosure sound complete? 6. ___

☐Yes

☐No

If NOT, why not?

_____

_____

_____

_____

7. Was there any evident lack of understanding about research? 7. ___

☐Yes

☐No

What misperceptions were there?

- ☐ _____
- ☐ _____
- ☐ _____
- ☐ _____
- ☐ _____
- ☐ _____

8. What reasons did the respondent give for participating in the research?

- ☐ _____
- ☐ _____
- ☐ _____
- ☐ _____
- ☐ _____
- ☐ _____
- ☐ _____
- ☐ _____
- ☐ _____
- ☐ _____
- ☐ _____

9. What type of study was the respondent participating in?

10. Were there any great quotes? If so, transcribe them FROM THE TAPE.

EXHIBIT O: IN-DEPTH INTERVIEW--CODING MANUAL

INSTRUCTIONS FOR CODING In-Depth INTERVIEWS FOR THE SUBJECT INTERVIEW STUDY (SIS)

Advisory Committee on
Human Radiation Experiments (ACHRE)

This document is a reference and training tool to be used by staff coding In-Depth interview data on research participation. There is plenty of space to elaborate based on discussions during training.

IN PREPARATION FOR TRAINING YOU WILL BE ASKED TO REVIEW 5 INTERVIEW TRANSCRIPTS. YOU WILL BE ASSIGNED 2 CODES AND ASKED TO PICK SOME EXCERPTS THAT EXEMPLIFY THE CODES DESCRIBED AND WRITE THEM IN THE "EXAMPLE" SPACE PROVIDED UNDER EACH CODE DESCRIPTION.

THE TWO CODES ASSIGNED TO YOU ARE:

1.

2.

INTERVIEWER NAME _____ PATIENT ID#_____

OVERVIEW

Global Codes, the final coding scheme for the Subject Interview Study (SIS) In-Depth interviews, reflect several rounds of review at the levels of conceptualization and implementation:

Global Codes have their origins in (1) the four original analytic domains of the SIS: general beliefs and perceptions about research, personal experiences and understanding of research, reasons for participating, and voluntariness of participation, (2) issues and concepts significant to respondents themselves as identified during a review of an initial set of completed transcripts, (3) additional topics of interest to the ACHRE as expressed during their review of proposed codes 3/17/95.

ACHRE and RTI staff have agreed to employ an intermediate level of coding, collapsing the former distinction between Domains and Codes presented in the interviewer training manual. Scaling back the number of final codes will facilitate timely processing of data for analysis, keep respondent comments and ideas as contextual as possible, and keep both the attention of the coder and the analyst on broad domains that have potential policy implications.

WHY CODE?

One of the challenges of qualitative data analysis is the sheer quantity of information to be analyzed. Coding provides a means of sifting through the data and sorting it in more manageable chunks. Analysts will then review the data by code and/or combinations of codes looking for themes, patterns and metaphors which encapsulate respondent perceptions as well as discrepancies.

HOW WILL CODES BE USED?

Once the hard-copy transcripts of the interviews are coded, they will be reviewed by other coders as a consistency check. Discrepancies in coding will be arbitrated by Rose Etheridge or Elissa Adair. Final codes will than be entered into a software package for the analysis of qualitative data. Reports will then be printed out which contains segments of text from all the different interviews with the same code.

HOW WILL CODING WORK?

Training will provide an opportunity to clarify coding concepts and procedures and cross-check between coders. After training, coders will receive a pack of interviews to code. Coded interviews will be returned to Rose. Instructions for use of typographic symbols to indicate which codes begin where on the hard copies should be followed to the letter. These instructions ease data processing considerably.

GENERAL RULES

Always code opposites together. If you can't figure out where a statement belongs, try to turn it around to its opposite and see if it will fit into one of the categories.

Always overcode. It is better to put both codes down if you have any question about which category is most appropriate.

INTERVIEWER NAME _____ PATIENT ID#_____

If the interviewer's question sheds light on the respondent's answer, code back to the question, even if the question is not immediately prior to the response.

TYPES OF CODES

There are two types of codes: labels and concepts. Labels are used to mark every instance of a certain thing in a text, like a term or experience. Concepts refer to a broader sequence of events or processes. All of the label codes described come with a set of key words. Whenever a key word occurs, CODE IT. Concept codes do not come with a set of labels. It is necessary for coders to have a clear idea of what ideas and research questions are encapsulated in each code. This document is to assist coders in understanding the concepts behind the codes.

SUMMARY OF CODES

The codes are as follows:

This code is about general, as compared to personal, commentary about the research process.

GEN: GENERAL APPRAISAL OF RESEARCH

This series of codes relate to how and why respondents became research participants. They include situational, motivational and personal characteristics.

PER: PERSONAL EXPERIENCE OF RESEARCH
BCM: BECOMING
ALT: ALTERNATIVES
VOL: VOLUNTARINESS
REAS: REASONS FOR PARTICIPATING
CON: CONSENT

These next two topics were chosen as important for understanding the participants' point of view as based on pilot data and preliminary review of interviews.

BB: BLURRED BOUNDARIES
TRU: TRUST

The next two codes are label codes. While they are likely to contain important concepts in regard to how participants perceive research, they are to be used as a label to mark the use of certain vocabulary in the text.

TRM: TERMS
RAD: RADIATION

The last and final code is to be used by you (the coders) for anything important that the above codes might have missed!

INTERVIEWER NAME _____ PATIENT ID#_____

NOTE: NOTEWORTHY

NOTES:

_____

_____

—

INTERVIEWER NAME _____ PATIENT ID#_____

GENERAL APPRAISAL OF RESEARCH (GEN)

TYPE OF CODE: Concept

What are respondents' attitudes about research, in general?

Encompasses respondent's belief structure regarding research, in general. This code is not appropriate for respondent's personal experience of research, but rather, what s/he thinks of research more generally. Potential overlaps: TRM, PER

Definitions of and/ or concrete descriptions of research.

Evaluative statements about research: good, bad, expensive, promising, exploitative, etc.

Concrete examples of benefits or detriments of research: advances knowledge, helps people, creates better treatments, etc.

Respondent's attempts to generalize about research from his/her own experience

EXAMPLE:

NOTES:

INTERVIEWER NAME _____ PATIENT ID#_____

PERSONAL EXPERIENCE (PER)

TYPE OF CODE: Concept

What has been the respondent's personal experience with research? Most importantly, were their experiences positive or negative? How so?

Considers respondent descriptions of his/her own experience participating in research, his/her own understanding of the particulars of the research, and his/her attitudes toward the research project they are/were in (e.g., beneficial, harmful, inconvenient). Some respondents may more readily use technical and medical details in describing their research experience, while others more readily convey the social, emotional, or moral aspects of their experience.

Evaluative statements regarding personal research experience: frightening, reassuring, beneficial, not helpful, inconvenient, etc.

Discussion of benefits (e.g., improved health, better treatment, hope, time) and/or detriments (e.g., risk, poor outcomes, bad side effects).

Discussion of the context for research participation experience: illness, social relationships (whether with intimates or professionals), institution, etc.

Discussion of how respondent was treated by research study staff.

Descriptions of research project in which respondent has participated, whether diagnostic, therapeutic, epidemiological, or survey. Also, respondent details regarding research particulars such as procedures, hospital visits, side effects, etc.

EXAMPLE:

_____

_____

_____

_____

_____

_____

_____

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NOTES:

_____

_____

INTERVIEWER NAME _____ PATIENT ID#_____

BECOMING A RESEARCH SUBJECT (BCM)

TYPE OF CODE: Concept

How did the respondent end up in the research project?

Encompasses the process (including decisions, actions, relationships, etc.) by which a respondent became a research subject in his/her own words. For some, becoming a subject may have been a matter of deciding, for others a matter of simply acting. While REAS focuses on the "why" of participation, BCM focuses on the "how." BCM is also sensitive to whether or not a respondent sees him or herself as an active or passive agent in the process of becoming a research subject. Potential overlaps: VOL, REAS, TRU, CON

Discussion of the sequence of events through which respondent ended up in what s/he considered to be a research project.

Description of steps respondent took to become a research participant:

"Thinking" steps such as acquiring information, weighing risks and benefits, weighing input from others, deciding to join and/or stay.

"Doing" steps such as seizing the only option available, joining the project.

References to any people to whom the respondent turned to for advice, information, comfort, or support with respect to research participation, whether providers, researchers, family members, friends, other patients, etc.

EXAMPLE:

NOTES:

INTERVIEWER NAME _____ PATIENT ID#_____

ALTERNATIVES (ALTS)

TYPE OF CODE: Concept

Did the respondent consider there to be any alternatives to research participation? If so, what were they? If not, why not?

Identifies excerpts in which the respondent discusses what alternatives to research participation, if any, were available to him or her or not, also what his/her experience would have been if s/he had not participated in research. This category will be most applicable to respondents who are or have been enrolled in therapeutic or diagnostic research rather than those in epidemiological or survey research.

Descriptions of medical alternatives available or not to the respondent: therapies, procedures, diagnostic techniques, medications, etc.

References to the fact that respondent had no other medical options or had exhausted all other options.

Respondent's account of being told what his/her alternatives to research would be; of who discussed alternatives with him/her.

Descriptions of a more philosophical nature, that is, what the patient would face if they did or did not participate in research: certain death, less time with family, hopelessness, certainty, uncertainty. etc.

EXAMPLE:

NOTES:

INTERVIEWER NAME _____ PATIENT ID#_____

VOLUNTARINESS (VOL)

TYPE OF CODE: Concept

Is voluntariness communicated and understood as an integral part of research practice? If so, how? If not, how not?

Captures the extent to which respondents believe they, as individuals, freely participated in research or not and considers instances in which a respondent felt pressure or coercion to join in or stay in research. "Pressure" could come from a number of sources: research staff, personal physician, family members. Voluntariness or lack of voluntariness may be expressed in different ways. Participants may describe a situation where they were given a choice, where they made a decision, or where they let things happen to them, etc. Potential overlaps: CON, BCM, TRU, REAS

Discussion of people who played a role in respondent's decision to join and stay in research or not (family, friends, other patients, research staff, personal physician, etc.).

Discussion of the decision was predominantly the respondent's own vs. predominantly someone else's.

Discussion of respondent's sense of freedom to join or decline research, request changes to treatment, leave in the middle of the study, ask for more information, etc.

Discussion of any pressure respondent felt to join or stay in the research study.

Discussions of extent to which respondent felt him/herself to be a willing research subject.

Descriptions of respondent's sense of control over his/her own destiny in research.

Discussion of respondent withdrawing from or altering treatment.

Remarks that respondent knew or did not know s/he had the option of declining research, modifying treatment, withdrawing.

EXAMPLE:

INTERVIEWER NAME _____ PATIENT ID#_____

NOTES:

INTERVIEWER NAME _____ PATIENT ID#_____

REASONS FOR PARTICIPATING AND CONTINUING IN RESEARCH (REAS)

TYPE OF CODE: Concept

Why do respondents' participate or not participate in research?

Covers motivations/incentives/disincentives for participating, not participating or continuing in research.
Potential overlaps: GEN, CON, BCM.

Descriptions of role that respondent's illness had in decision to participate (e.g., severity, type)

Remarks regarding the potential health benefits or side effects of research treatment.

Caution: Code description of side effects of research treatment if it was a reason respondent stopped. If respondent is just talking about side effects that happened, then excerpt should be coded PER.

Discussion of how money matters affected decision to join or stay (e.g., insurance, drug cost, payment for participation).

Comments regarding a desire to help others (e.g., patients, people with same disease, doctors, researchers, "society").

Discussion of personal things to be gained through participation (e.g., hope, a future, a sense of control, more time with family).

EXAMPLE:

NOTES:

INTERVIEWER NAME _____ PATIENT ID#_____

CONSENT (CON)

TYPE OF CODE: Concept

How do respondents' describe and assess the process through which they are included as part of research?

Encompasses the respondent's experience with and appraisal of the consent process from recruitment and information exchange, to agreeing to participate and signing a consent form. CON considers respondent's descriptions of the formal consent process as well as anything significant to the respondent's own definition of consent. Potential overlaps: BCM, VOL, TRU

Respondent's description of the consent process: what it is, how it works, who plays what role, what is the final outcome.

Descriptions about how respondents were approached, who approached them, how research was initially described, how consent was obtained.

Any evaluative remarks regarding a good or bad means of acquiring consent.

Description of patient's experience with and subjective assessment of the formal consent process with its emphasis on information exchange and decision-making.

Remarks as to what role "information" played in patient's agreeing to participate -- having conversations with staff, forms, reading a consent form.

Recollections of having signed a consent form.

Details about the meaning or value of the "consent form" to the patient.

Remarks indicative of respondent's own definition of "consent" or model of "consent" that poses as an alternative to or reinforcement of institutionalized process.

EXAMPLE:

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NOTES:

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INTERVIEWER NAME _____ PATIENT ID#_____

BLURRED BOUNDARIES (BB)

TYPE OF CODE: Concept

Is the research experience distinct from the respondents' experiences of illness and health care? If it is distinct, where is it distinct? If it is blurred, where is it blurred?

Covers the extent to which research participation, in the respondent's mind, is distinct or not from his/her illness experience and/or experience with the health care system. Considers at what point the boundaries among research, illness, and health care are distinct or blurred: research vs. treatment; researcher vs. provider, subject vs. patient, research institution vs. non-research institution; medical condition vs. side effects of experimental treatments. Potential overlaps: All Global Codes

EXAMPLE:

NOTES:

INTERVIEWER NAME _____ PATIENT ID#_____

TRUST (TRU)

TYPE OF CODE: Concept

On what types of individuals, institutions, technologies, or information do respondents rely as research subjects? Which do they trust and why? Which don't they trust and why?

Considers any commentary regarding the respondent's trust or distrust as well as confidence or lack thereof, in the people and processes of research, such as institutions (e.g., FDA, drug companies, hospitals, universities, IRB), professionals (researchers and health care providers), medical technology, and information. Potential overlaps: REAS, BCM, PER

Descriptions of institutional mechanisms (e.g., FDA, IRB, "the market") and/or moral mechanisms (e.g., doctor's obligation to help patients) in place to protect research subjects. For example,

How doctors or the "system" wouldn't let you try a drug that could be harmful.

How a respondent couldn't have the placebo because she trusts his/her doctor.

Discussion regarding the validity, reliability of information provided to respondent.

Discussions of the interests held by the various parties involved in research (subjects, researchers, research institutions, regulatory agencies, drug companies).

Discussion of respondent's relationships with physicians and research staff.

EXAMPLE:

_____

_____

_____

_____

INTERVIEWER NAME _____ PATIENT ID#_____

NOTES:

INTERVIEWER NAME _____ PATIENT ID#_____

TERMS (TRM)

TYPE OF CODE: Label and Concept

KEY WORDS: (medical) research, study, clinical trial, (medical) experiment, (clinical) investigation, protocol, program, etc.

What words do participants use to refer to research? How do they distinguish between kinds of research in their vocabulary and narrative?

As a labelling code, **Terms** marks any words or the phrases the respondent uses for "research" (e.g., study, experiment, trial, clinical investigation) as well as concrete examples. As a conceptual code, **Terms** covers the patient's own categories or gradations of research activities and attendant values (e.g., "Experiments are risky; their results are uncertain." "Studies don't involve invasive procedures." "A clinical trial uses tried and true methods, so I wasn't worried about signing up."). Potential overlaps: TRU, GEN, PER

Label:

Any word used for research however idiosyncratic

Definitions and/or concrete examples of research terms:

References to respondent's own categories of research.

Descriptions of the range of research activities and their distinctive traits.

EXAMPLE:

_____

_____

_____

_____

_____

NOTES:

_____

_____

_____

_____

—

INTERVIEWER NAME _____ PATIENT ID#_____

RADIATION (RAD)

TYPE OF CODE: Label and Concept

KEY WORDS: x-ray, radiation, dyes, cobalt, radiologist, barium

As a labelling code, **Radiation** identifies any respondent commentary on radiation, whether related to research or not. As a conceptual code, **Radiation** encompasses the respondent's feelings toward radiation, its use in research in general, and its role in his/her decision to take part in a research project or not. Excerpts will assist in analysis of comparisons between radiation-research subjects and nonradiation-research subjects, and for evaluating general attitudes toward radiation. Potential overlaps: All Global Codes.

Label:

Any use of words or phrases regarding radiation (x-ray, dyes, cobalt, radiologist, barium, etc.) If unsure whether or not a procedure involves radiation, go ahead and code it.

Concepts:

Descriptions of any experience the respondent has had with radiation, whether research-related or not.

Commentary regarding the value (positive or negative) of medical uses of radiation.

Feelings toward radiation, in general.

EXAMPLE:

_____

_____

_____

NOTES:

INTERVIEWER NAME _____ PATIENT ID#_____

_____

_____

NOTEWORTHY (NOTE)

TYPE OF CODE: Concept

Provides coder the option of coding an extraordinary passage for which no unique code exists. As a miscellaneous category, NOTE empowers coders to identify transcript excerpts worthy of consideration during analysis. Coders, however, should use this code sparingly to retain its potential value to analysis, i.e., coders should avoid using this code as a dumping ground for passages more thoughtfully included in existing categories.

> Passages of text that do not fit into existing codes, but which command attention as concepts or issues significant to final analysis and policy questions.

EXAMPLE:

NOTES:

EXHIBIT P: DATA ENTRY MANUAL

OVERVIEW

This manual provides documentation of the purpose, procedures and methods for entering codes for the In-Depth Interviews for the Subject Interview Study sponsored by the Advisory Committee on Human Radiation Experiments.

About the Software

"TALLY" is the qualitative data analysis software package that we will use for this project. The software is designed to sort textual data. It captures ideas and concepts from transcripts of interviews using codes input directly to the electronic text file. TALLY can extract coded text from the electronic text file, count code frequency and generate reports based on the coded information.

Basic TALLY Elements

For our purposes, TALLY has three parts: (a) a hard copy of the original interview with handwritten codes identifying specific ideas or concepts, and (b) an electronic file of the original transcript, and (c) a finished coded data file.

Basics to Entering the Codes

With each PC diskette, you will receive hard copies of the coded interviews. The hard copy will be double-spaced with handwritten codes and brackets written just above the typed text. It will be your job to type in the hand-written brackets and codes exactly as they appear on the hard copy into the TALLY data entry screen.

Data Management

The In-Depth interviews were recorded, transcribed, and stored as ASCII files to be used in TALLY. There are five (5) interviews per PC diskette. The transcribed data files have a unique client ID as their file name followed by the extension .TXT.

An additional file, created by TALLY, is the file you will use to code the transcribed data file. It is a duplicate of the transcribed file with a different extension (.DAT) to separate it from the original. Both the text file and the duplicate file for coding are provided on the diskette. For example,

334202-9.txt	=	name of a transcribed data file.
334202-9.dat	=	name of the duplicate, transcribed file to be used for coding.

Batch Information Sheet

On the top of each batch, there will be a form to fill out for each of the interviews. It will require you to sign your initials next to each of the files you code, give the date you coded the file, how long it took you to code the file, and the outcome of the coded document.

There will be two options for the outcome field. Check the field if the document was coded and saved without error. Place an "I", for incomplete, in the field if the file was coded and not saved without error.

TECHNICAL

Symbols

The following symbols are used here to denote specific keyboard actions when typing in commands or executing commands:

☞ This symbol means to leave one space between text.

☜ This symbol means to press the return/enter key to execute a command.

Executing the TALLY Software

TALLY has been loaded on the C: drive of the PC in a subdirectory called TALLY. To execute the TALLY software, you must be in the subdirectory TALLY. To begin a TALLY session, type "TALLY". For example,

at the C:> prompt, type ..... CD ☞ TALLY ☜

at the C:\TALLY> prompt, type ..... TALLY ☜

A screen will appear with a menu bar across the top. The menu bar includes such topics as (a) Analysis, (b) Reports, (c) Mnemonics, (d) Utilities, and (e) Quit Tally. You will only be concerned with the "Analysis" menu.

To exit any TALLY session without saving any work, press the escape key until you return to the C:\TALLY> prompt.

Analysis Menu

At start-up, the Analysis menu will be highlighted by default. To pull down the menu, use your return/enter key. A menu including the following topics will appear: (a) Mnemonics Set, (b) Text File, (c) Codings File, (d) Editor, and (e) Hard Copy. You will only be concerned with the first four topic items.

You must execute each of the first four topics, in sequential order, in order to complete the data entry for an interview. You begin with the Mnemonics Set.

Mnemonics Set

The Mnemonics Set provides TALLY the name of the file holding the codes to be used during data entry. There will only be one file of this sort in the TALLY subdirectory. The file is named PILOT.SET, and you must choose this file at the beginning of each TALLY session.

To choose this file, highlight the Mnemonics Set topic item, then press your return/enter key (a

dialog box will appear). Two dots (..) will be highlighted in the dialog box; use your right arrow key to highlight the PILOT.SET file, and press your return/enter key to return to the topic box. Now you will be ready to move on to the Text File option.

Text File

The Text File option provides TALLY with the name of the interview file you want to code. Choose this item by highlighting the option and pressing the return/enter key. A dialog box will appear showing no files. You must tell TALLY where the files are located to see a listing of the five available interviews to code. Do this by typing A:\ and press your return/enter key.

Five files will appear in the dialog box.

Choose the file you wish to code, then press your return/enter key. You will return to the topic box and be ready to move on to the Codings File option.

Codings File

The Codings File option provides TALLY with the name of the file used to hold the coded interview. Choose this item by highlighting the option and pressing the return/enter key. Similar to the Text File option, a dialog box will appear showing no files. Type A:\ and press the return/enter key.

Five files will appear in the dialog box. Choose the file that IDENTICALLY MATCHES the Text File name you are currently using. Press the return/enter key to return to the topic box. Now you will be ready to move on to the Editor option.

Editor

The Editor is where you will begin to actually enter the codes into the electronic file as they appear on the hard copy. Only after you have completed the first three steps can you highlight this option and press the return/enter key.

A copy of the interview will appear on the screen. If an error occurs and either the screen is blank or a different file appears, redo steps 1, 2, and 3 (i.e., retrace your steps from the Mnemonics Set, the Text File, and the Codings File). Make sure you have asked for identical files and the problem should be resolved.

Moving from left to right, type in the brackets and codes, exactly as they appear on the hard copy, on the blank line above the text. Use your F2 key for a selection of codes to be placed above the text, or type the code.

If typing the codes above the texts proves to be easiest for you, rather than using your F2 key to have TALLY insert the code, be sure you do not type the codes wrong. TALLY will not report errors for mistyped codes. Mistyped codes are not used in all TALLY reporting and data can be lost. Therefore, it is very important codes are placed and spelled properly.

Brackets are very important in this process. They provide TALLY with the beginning and ending of the concept to be coded. For every left bracket, you must have a right bracket. If this does not occur, TALLY will give you an error when you try to save your work. You must resolve unbalanced brackets before the interview can be used for TALLY analysis.

Exiting the Editor

After you have finished coding the interview, exit the editor by holding down the Alt key and X letter key at the same time. If you must exit the coding processs before you are finished use your Alt X combination of keys to save your work and exit TALLY. To return to your previously coded file, follow steps 1, 2, and 3 as if you are beginning a new case and you can begin where you left off. Notice there is a line counter at the top of the menu bar in TALLY to quickly find the line number where you left off.

Errors When Exiting the Editor

If TALLY indicates there is an error when saving your work, first try to resolve the error (most likely unbalanced brackets). Should you not be able to resolve an error, continue to save your work in the normal manner and flag the interview as Incomplete on the batch information sheet.

Brief Technical Overview

At the C:\> prompt

CD ☞ TALLY ..... ☜
TALLY ..... ☜
Highlight Analysis ..... ☜
Highlight Mnemonics Set ..... ☜
Highlight PILOT.SET ..... ☜
Highlight Text File ..... ☜
Type a: ..... ☜
Highlight desired Text File ..... ☜
Highlight Codings File ..... ☜
Type a: ..... ☜
Highlight desired Codings File ..... ☜
Highlight Editor ..... ☜
Enter codes
Press ALT X simultaneously to save work
Complete batch information sheet

Errors when saving:

- Do not continue the saving process and return to document.
- Try and resolve any unbalanced brackets and resave.
- If there are still errors, flag the interview on the batch sheet.

Codes (Mnemonic Set)

GEN	General Appraisal of Research
PER	Personal Experience with Research
REAS	Reasons for Participating

VOL	Voluntariness
CON	Consent
BCM	Becoming
TRU	Trust
BB	Blurred Boundaries
TRM	Terms
RAD	Radiation
ALT	Alternatives
NOTE	Noteworthy
ID	Respondent ID

6

OUTSIDE VIEWS ON THE CURRENT SYSTEM FOR THE PROTECTION OF HUMAN SUBJECTS

To augment our understanding of the important issues in the oversight of human subject research, the Advisory Committee sought outside views on the current system for protection of research subjects. Our invitation for written comments on the oversight system was extended to four categories of individuals:

1. chairs of institutional committees responsible for the review of all research involving human subjects at their institutions (IRB chairs),
2. chairs of institutional committees that specifically review the use of radioactive materials and radiation at their institutions (radiation safety committee or radioactive drug research committee chairs),
3. radiation researchers, and
4. heads of professional societies whose membership employs radiation or radioactive materials in their professional activities (e.g., nuclear medicine, radiological, and health physics societies).

This selection of individuals was initially based on the institutions included in the Advisory Committee's Research Proposal Review Project (see chapter 15 of the Advisory Committee's final report), and was enhanced by suggestions from members of the committee. The selection was meant to represent large research centers and professional groups intimately involved in protection of research subjects and radiation safety policies, but it was by no means an exhaustive or highly varied sample. It was intended to help us arrive at a general sense of the important issues from those involved with them on a daily basis.

We asked respondents for their thoughts on the adequacy of the current oversight system and the institutional review board (IRB) process, especially with respect to research involving radiation. The following issues were of particular interest to the Advisory Committee:

- aspects of the current system for the protection of the rights and interests of research subjects believed to be working well;
- aspects of the current system believed to be in need of change;
- the level of risk in research involving radiation, and the communication of this risk to prospective

research subjects;
- subject selection, generally;
- radiation research, generally; and
- recommendations, if any, for changing current practices and requirements in order to improve them.

A representative sample of our request letters are reprinted in exhibit A at the end of this chapter.

We received thoughtful responses that helped inform our development of recommendations concerning changes to current policies for the protection of human subjects. In this chapter we have reproduced in their entirety 25 of the letters that the Advisory Committee received in response to this inquiry. (See table 1 for a list of the respondents and their affiliations; see exhibit B for the reprinted letters.) In addition, a number of individuals responded by sending us copies of documents that have been published elsewhere; we have included the citations for these documents (see table 2). We received written permission from the authors to reprint the correspondence included in this chapter. As of the date of this publication we had not received responses to our requests for permission to publish from the other respondents. However, these additional responses remain a part of the Committee's public record stored at the National Archives.

Table 1--Authors of Letters Reprinted in Exhibit B

S. James Adelstein
Paul C. Cabot Professor of Medical Biophysics
Harvard Medical School
Boston, MA

Max L. Baker, Ph.D.
Professor of Radiology
University of Arkansas for Medical Sciences
Little Rock, AK

Leonard S. Bushnell, M.D.
Chairman, Committee on Clinical Investigations, New Procedures, and New Forms of Therapy
Beth Israel Hospital
Boston, MA

Arthur Caplan, Ph.D.
Director, Center for Bioethics, & Trustee Professor of Bioethics
University of Pennsylvania Medical Center
Philadelphia, PA

J. D. Chapman, Ph.D.
Senior Member, Department of Radiation Oncology
Fox Chase Cancer Center
Philadelphia, PA

Richard D. Cummings, M.S.
Radiation Safety Officer and Director of Health Physics Department
Wayne State University
Detroit, MI

John J. Curry
Executive Director
American College of Radiology
Reston, VA

Helen H. Evans, Ph.D.
President, Radiation Research Society (1994-1995)
Professor of Radiology
Case Western Reserve University
Cleveland, OH

S. John Gatley, Ph.D.
Research Scientist
Brookhaven National Laboratory
Upton, NY

Marvin Goldman, Ph.D.
President, Radiation Research Society (1994-1995)
Professor Emeritus of Radiological Sciences
University of California, Davis
Davis, CA

Michael M. Graham, Ph.D., M.D.
Chairman of Radiation Safety Committee and Professor of Radiology (Nuclear Medicine)
University of Washington Medical Center
Seattle, WA

Thomas R. Hendrix
Professor of Medicine and Chairman, Joint Committee on Clinical Investigation
Johns Hopkins University
Baltimore, MD

Christopher C. Kuni, M.D.
Professor, Radiology and Co-Chair, IRB
University of Minnesota Hospital and Clinic
Minneapolis, MN

Paul. J. Lavely
Radiation Safety Officer and Director, Office of Radiation Safety
University of California, Berkeley
Berkeley, CA

Robert J. Levine, M.D.
Professor of Medicine
Yale University School of Medicine
New Haven, CT

Curtis L. Meinert, Ph.D.
Professor, Epidemiology
Center for Clinical Trials
The Johns Hopkins University
Baltimore, MD

David D. Oakes, M.D., F.A.C.S.
Associate Professor of Surgery
Stanford University School of Medicine
San Jose, CA

Theodore L. Phillips, M.D.
Professor and Chairman, Department of Radiation Oncology
University of California, San Francisco
San Francisco, CA

Ernest D. Prentice, Ph.D.
Associate Dean for Research
University of Nebraska Medical Center
Omaha, NE

Austin Ranney
Chair, Committee for Protection of Human Subjects
University of California, Berkeley
Berkeley, CA

James W. Ryan, M.D.
Associate Professor of Clinical Radiology and Chairman of the Human Use Committee for Radioisotopes
University of Chicago Medical Center
Chicago, IL

Gene Saccomanno, Ph.D., M.D.
Pathologist, Cancer Research Institute & Chairman, IRB
St. Mary's Hospital Cancer Research Institute
Grand Junction, CO

Mark H. Selikson, Ph.D.
Director, Radiation Safety Office & Chairman, RDRC
University of Pennsylvania
Philadelphia, PA

Barry A. Siegel, M.D.
Chairman, Radioactive Drug Research Committee
Washington University School of Medicine
St. Louis, MO

Ralph W. Trottier, Ph.D., J.D.
Professor, Chairman, IRB
Morehouse School of Medicine
Atlanta, GA

Supplemental Volume 1

Table 2--Publications Provided to the Advisory Committee

Report of the Ad Hoc (Harvard) University Committee to Review Aspects of Human Subjects Research, January 1995.
Beth Israel Hospital, "A Historical Review of Radioisotope Use at Beth Israel Hospital," May 1994.
Frank P. Castronovo, Jr., "An Attempt to Standardize the Radiodiagnostic Risk Statement in an Institutional Review Board Consent Form," *Investigative Radiology* 28 (1993): 533-538.
Ken Mossman, "The Human Radiation Experiments: The Real Issues," *Health Physics* 68 (1995): 757-760.

EXHIBIT A

Sample Advisory Committee Request Letters

ADVISORY COMMITTEE ON HUMAN RADIATION EXPERIMENTS
1726 M STREET, N.W., SUITE 600
WASHINGTON, D.C. 20036

Dear

As you may know, the Advisory Committee on Human Radiation Experiments was appointed by President Clinton to examine federally sponsored or conducted research on human subjects with ionizing radiation from the 1940s to the present. The Committee has explored the history of ethics standards, practices and policies, and we will make recommendations concerning the design and implementation of current policies and regulations.

The Committee has been grappling with these difficult issues since last April. Over the next several months, we must prepare our recommendations for the Clinton Administration. With this in mind, we write to you in your capacity as the chair of an institutional committee that reviews radiation research. In particular, we hope that you will share your views on calculating radiation risk and on communicating radiation risk to prospective research subjects. The Committee would also like to know how, if at all, you would change current practices and requirements in order to improve them. Your contribution would enhance this Committee's understanding of the way in which radiation research is currently conducted in this country. All comments will become a part of the Committee's public record.

We would welcome any thoughts, however detailed or brief, and believe that your participation in this endeavor would be an important public service. However, time is regrettably short. Thus, for your comments to influence the Committee's deliberations, we must have them as soon as possible, but no later than March 21st. Please send your comments to the Advisory Committee's above address to the attention of Denise Holmes.

Thank you in advance for your kind assistance.

Sincerely,

Ruth Faden

Ruth R. Faden, Ph.D., M.P.H.
Chair

ADVISORY COMMITTEE ON HUMAN RADIATION EXPERIMENTS
1726 M STREET, N.W., SUITE 600
WASHINGTON, D.C. 20036

Dear

As you may know, the Advisory Committee on Human Radiation Experiments was appointed by President Clinton to examine federally sponsored or conducted research on human subjects with ionizing radiation from the 1940s to the present. While the Committee's mandate specifies radiation research, its review necessarily contemplates the ethical conduct of all human subjects research. We have explored the history of ethics standards, practices and policies, and we will make recommendations concerning the design and implementation of current policies and regulations.

The Committee has been grappling with these difficult questions since last April. Over the next several months, we must prepare our recommendations for the Administration. It is with this in mind that we write to you in your capacity as chair of an IRB that reviews research on human subjects. In particular, we hope that you will share your views on the aspects of the current system for protection of rights and interests of research subjects that you believe are working well, as well as those aspects that you believe are in need of change. We would welcome comments on what (if anything) you would do differently if you were charged with the responsibility of ensuring the protection of the rights and interests of human subjects of medical research. Any thoughts about radiation research in particular would be especially welcome. Your contribution would enhance this Committee's understanding of the way in which research currently is conducted in the American health care system. All comments will become a part of the Committee's public record.

We would welcome any thoughts, however detailed or brief, and believe that your participation in this endeavor would be an important public service. However, time is regrettably short. Thus, for your comments to influence the Committee's deliberations, we must have them as soon as possible, but no later than February 24th. Please send your comments to the Advisory Committee's above address to the attention of Denise Holmes.

Thank you in advance for your kind assistance.

Sincerely,

Ruth Faden

Ruth R. Faden, Ph.D., M.P.H.
Chair

EXHIBIT B

Letters Received in Response to the Advisory Committee's Request

Harvard Medical School

25 Shattuck Street
Boston, Massachusetts 02115
TEL (617) 432-1535, 1536
FAX (617) 432-4043

Office of the Executive Dean
for Academic Programs

February 24, 1995

Ruth R. Faden, Ph.D., M.P.H.
Chair
Advisory Committee on Human
Radiation Experiments
1726 M Street, N.W., Suite 600
Washington, D.C. 20036

Dear Dr. Faden,

Through Denise Holmes, I have received your letter inquiring as to my views on the current system for protection of rights and interests of research subjects.

My views in this matter are best expressed in the Report of the Ad Hoc (Harvard) University Committee to Review Aspects of Human Subjects Research submitted to the Provost of Harvard University in January 1995. I believe that Ms. Margaret Dale has sent a copy of the report to your office.

In addition, I have attached materials on presenting radiodiagnostic risks to potential human research subjects by my colleague Frank P. Castronovo, Jr., that may be of interest to your committee.

Thank you for soliciting my views. I wish you well in your endeavors.

Yours sincerely,

S. James Adelstein, M.D., Ph.D.
Paul C. Cabot Professor of
Medical Biophysics

encl.

SJA/ss

EPARTMENT OF
RADIOLOGY

4301 West Markham, Slot 556
Little Rock, Arkansas 72205-7199
501/686-5740; Fax: 501/686-6900

Ernest J. Ferris, M.D.
Professor and Chairman

Steven K. Teplick, M.D.
Professor and Vice Chairman

Tereska L. Angtuaco, M.D.
Director, Division of Imaging

Richard E. Leithiser, M.D.
Director, Residency Training Program

Joanna J. Seibert, M.D.
Professor of Radiology
Director, Division of Pediatric Radiology

Janice Allison, M.D.
Edgardo J.C. Angtuaco, M.D.
Head, Neuroradiology
Max L. Baker, Ph.D.
C. Barry Buckner, M.D.
Head, Chest Radiology
Wilma C. Diner, M.D.
John F. Eldt, M.D.
Richard Fizzandolph, M.D.
Charles M. Glasier, M.D.
David Harshfield, M.D.
Head, VA Radiology
John G. Holder, M.D.
Charles A. James, M.D.
Sarah G. Klein, M.D.
Richard A. Komoroski, Ph.D.
E. Lynn McGuire, M.S.
David McFarland, M.D.
Chief, Cardiovascular and
Interventional Radiology
Alfred J. Moss, Jr., Ph.D.
William A. Nagle, Ph.D.
David Newbern, M.D.
Joseph A. Norton, M.D.
Naresh Patel, M.D.
Gary Purnell, M.D.
Hemendra R. Shah, M.D.
Head, Body CT and MRI
Nita N. Sheth, M.D.
Warren Stringer, M.D.
Kathy Thomas, M.D.
James Vandergrift, M.S.
Theodora Vanderzalm, M.D.

UAMS MEDICAL CENTER

March 13, 1995

Ms. Denise Holmes
Advisory Committee on Human Radiation Experiments
1726 M Street, N.W., Suite 600
Washington, D.C.

Dear Ms. Holmes:

I am responding to the letter of 7 March 1995 from Dr. Ruth Fader regarding human experimentation involving radiation exposure.

At the University of Arkansas for Medical Sciences, all research involving human subjects is reviewed by the institution's Human Research Advisory Committee. The Radiation Safety Committee reviews protocols for this committee in view of the safe use of radiation--both for the patient and the research worker. Advisory information is often given as well in the wording of the consent form to better communicate radiation exposure information to the patient.

In the wording of the consent form, we try to provide the exposure information in a manner to which the patient can relate. For example, procedures involving lower exposures may be compared to a common radiographic procedure such as a chest X-ray or a natural background radiation exposure. Procedures with higher levels of exposures are usually placed in the context of occupational exposure levels or permissible doses.

Assessment of risk is more difficult to determine, particularly a numerical value for it. The current value of 0.08% per rem from BEIR V is of use. ICRP publication 62, *Radiological Protection in Biomedical Research*, also provides some risk categories. When providing values for risk of radiation exposures, I believe that it is important to provide value for other risks associated with medical care (surgery, anesthesia, etc.) as well as overall risks of other potential effects--normal incidence of cancer for example.

Finally, the paper by T. R. Hendix, "Human Investigation and Informed Consent," *American Journal of Roentgenology* 140:600-601, March, 1983, gives some model statements.

Hopefully this will provide you with some information regarding this institution's handling of human research involving radiation. You might also wish to contact Dr. Robert Abernathy, the Chairman of the Human Research Advisory Committee at Slot 598, at the above address. If I can provide you with other information, please contact me.

Sincerely,

Max L. Baker, Ph.D.
Professor of Radiology
Chairman, Radiation Safety Committee

MLB/jdm

copies: Carol Price, M.S., Radiation Safety Officer, UAMS

Robert S. Abernathy, M.D., Ph.D., Chairman, Human Research Advisory Committee, UAMS

HARVARD MEDICAL SCHOOL

BETH ISRAEL HOSPITAL

LEONARD S. BUSHNELL, M.D.
Associate Professor
of Anesthesia

10 February 1995

DEPARTMENT OF ANESTHESIA
AND CRITICAL CARE
Beth Israel Hospital
Boston, Massachusetts 02215
(617) 735-3127
FAX (617) 735-5013

Advisory Committee on Human Radiation Experiments
1726 M Street, N.W., Suite 600
Washington, D. C. 20036

Ladies and Gentlemen:

I write in response to Dr. Faden's letter of February 7. The eighth sentence of her letter is puzzling. IRB's are currently "charged with the responsibility of insuring the protection of the rights and interests of human subjects of medical research". I think the current system for protection of rights and interests of research subjects works well. Our thoughts about radiation research are in the enclosed booklet.

Sincerely yours,

Leonard S. Bushnell, M. D.
Associate Professor of Anesthesiology, Harvard Medical School
Chairman, Committee on Clinical Investigations
Beth Israel Hospital

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FOX CHASE
CANCER CENTER

J. Donald Chapman, Ph.D.
Director, Tumor Biology and Biophysics Section
Department of Radiation Oncology

7701 Burholme Avenue
Philadelphia, Pennsylvania 19111-2497
215 728 4305
FAX 215 728 4333

March 13, 1995

Ruth R. Faden, Ph.D., M.P.H.
Chairperson
Advisory Committee on Human Radiation Experiments
1726 M. Street, N.W., Suite 600
Washington, D.C. 20036

Dear Dr. Faden:

In response to your telefax of March 7, 1995 I submit the following comments. The Laboratory Isotope and Radiation Safety Committee which I chair at the Fox Chase Cancer Center oversees the use of isotopes and sealed research sources in laboratory research. These studies specifically involve molecules, cell lines in tissue culture and rodent tumor and normal tissues. Our practices and procedures are regulated by the NRC and are subject to annual inspection and review.

All clinical research involving human subjects (both diagnostic and therapeutic) are reviewed by the Clinical Research Advisory Committee (on which I sit) before submission to the local IRB for approval. A few clinical protocols involve the systemic administration of radioisotope-containing compounds to investigate tumor location and biology. The vast majority of radiation research protocols reviewed by the Clinical Research Review Committee involve modified radiotherapy to produce improved local control and tumor cures. About half of these research protocols are FCCC-investigator initiated while the other half are proposed by cooperative clinical trial groups (mainly the RTOG). It is my opinion that our local procedures for calculating the radiation risk involved in such research protocols and communicating these risks to prospective patients through consent forms are more than adequate. The cooperative clinical trials groups, and the RTOG, in particular, have served a most important role in educating their participating institutions and staff about the ethics associated with clinical research and communicating radiation risks to prospective patients. Most clinical trials proposed in the 1990's include stopping rules which protect against adverse effects in research subjects and to terminate procedures which show little promise of benefit to patients.

I am confident that the procedures developed by the Clinical Research Review Committee and the IRB of the FCCC fully protect potential research subjects from adverse radiation risk with excellent procedures of informed consent.

Yours sincerely,

J.D. Chapman, Ph.D.
Chairman, Laboratory Radiation Safety Committee
Fox Chase Cancer Center

JDC/ac

UNIVERSITY OF PENNSYLVANIA MEDICAL CENTER

University of Pennsylvania School of Medicine
Hospital of the University of Pennsylvania

Arthur L. Caplan, Ph.D.
Director

Center for Bioethics

FEB 21 1995

February 14, 1995

Ruth R. Faden, Ph.D., M.P.H.
Chair
Advisory Committee on Human Radiation Experiments
1726 M Street, NW, Suite 600
Washington, D.C. 20036

Dear Dr. Faden:

I have been asked by our IRB Chair, Karl Rickles, M.D., to respond to your letter of February 7. I serve on one of the three IRBs here at the University of Pennsylvania Medical Center, and in that role have had the opportunity to consider the issues you raise in your letter. I have also spoken to a number of other IRB members here at Penn to ascertain their feelings as to the aspects of the current IRB system that work well and those that require change.

Among the things the IRBs now do well are; the review of informed consent forms, the insistence on disclosure to prospective subjects of their right to withdraw from a study and their rights vis-a-vis injuries and compensation. Most of my colleagues feel that IRB members, here at Penn, try their best to make sure that subjects know that they are under no obligation to participate in research and that their options and alternatives are made known to them.

The main areas where improvement seems in order are; in the monitoring of ongoing research, the need to expedite minor forms of experimentation, the need to speed the process, the need to find better ways to handle the issue of adverse event reporting and the need to articulate better protections for vulnerable populations of subjects, particularly the mentally ill.

Monitoring of ongoing research to pinpoint problems that do or do not arise is not adequate. IRBs receive forms from researchers, but I and some of my colleagues believe that we are not doing a good job debriefing subjects who have been in research. Nor is there much in the way of good research to show that IRBs correctly pinpoint the issues that matter to the actual subjects of research.

IRBs, including ours, are still overloaded with work. There are many similar sorts of experiments which do not involve highly invasive or risky interventions. Some form of standard protocol and review seems to be in order, promulgated by the Federal Government for standard, low-risk research.

Adverse event reports take up a great deal of our time at Penn. Yet the monitoring of these events is close to worthless since we rarely have enough information about exactly what was going on to make a determination of whether an adverse event is troublesome or not. Some other mechanism needs to be found for handling this problem.

University City Science Center • 3401 Market Street, Suite 320 • Philadelphia, PA 19104-3308 • 215-898-7136 • FAX: 215-573-3035

University of Pennsylvania Health System

Protections for vulnerable populations are not what they should be. We often receive requests for research in emergency room contexts, on psychiatrically impaired subjects, or on senile subjects. We remain uncertain how to weigh risks and benefits in these groups or how to handle proxy consent when that is needed. More guidance to IRBs on these matters is long overdue.

I hope these comments prove useful to you. I and my colleagues are looking forward to learning about the findings of your advisory committee.

Sincerely,

Arthur Caplan, Ph.D.
Director, Center for Bioethics
Trustee Professor of Bioethics

AC/jc

cc: Karl Rickels, M.D.

• State University

Health Physics-Radiation Control
645 Mullett
Detroit, Michigan 48226

March 14, 1995

Ms. Denise Homes
Advisory Committee on Human Radiation Experiments
1726 M. Street, N.W. Suite 600
Washington, D.C. 20036

Dear Ms. Homes:

I am in receipt of your letter dated March 7, 1995 regarding my thoughts on practices and policies on Human Radiation Experiments for your Committee's deliberations.

Here at Wayne State University, we do not conduct human radiation experiments and to my knowledge, have not done so for many years. We do have a Radiation Safety and Radioisotope Committee that meets quarterly to review research protocols with the use of radioactive materials in vitro.

I might suggest you contact the national Health Physics Society which I'm sure could supply invaluable information regarding this subject. The society may be contacted at (703) 790-1745 via a Mr. Richard Burk Jr. In addition, Dr. Kenneth L. Mossman, past president of the Society, could possibly add valuable input to this subject. He may be contacted at the Arizona State University where he is the Assistant Vice President for Research.

I hope I have supplied some useful information and avenues to pursue for your committees decision making policies.

If I may be of further information, please feel free to contact me at (313) 577-1255.

Sincerely,

Richard D. Cummings

Richard D. Cummings, M.S.
Wayne State University
Health Physics Department
645 Mullett
Detroit, MI 48226

800

John J. Curry
Executive Director

April 17, 1995

Ruth R. Fader, Ph.D., MPH
Chair
Advisory Committee on Human Radiation Experiments
1726 M. Street, N.W., Suite 600
Washington, DC 20036

Dear Dr. Fader:

On behalf of the over 29,000 physician and physicist members of the American College of Radiology (ACR), we appreciate the opportunity to comment on calculating radiation risk and on communicating radiation risk to prospective research subjects.

In general, the ACR concurs with the policies developed by the National Council on Radiation Protection and Measurements (NCRP), specifically, in the recommendation that all radiation exposure should be done by effective dose equivalent and specific organ systems should be compared. We also agree that probability of causation should not be used in this setting. Radiation risk is unique and should only be compared to other types of radiation risks, not to other types of exposure. To this end, the College would commend to the Committee's attention the following publications:

- NCRP Report, Number 115, (1993) as it relates to new human risk estimates for cancer mortality, risk-projection models and derivation of risk at low dose.
- NCRP Report, Number 116, (1993). A summary of modifications from the Council's earlier recommendations on limits for exposure to ionizing radiation (NCRP 1987) can be found in section 19 of this report.
- NCRP Report, Number 117, (1993) as it relates to research needs in the field of radiation protection. In particular, the discussion in section 5.3 regarding the public perception of radiation risk and the need for better communication of this risk.

We would also recommend to the Advisory Committee two policy summaries from the International Commission on Radiological Protection (ICRP). The College supports the ICRP summaries for "Protection of the Patient in Diagnostic Radiology" and "Protection of the Patient in Nuclear Medicine" which are based on the following principles:

1) an individual should not be exposed to radiation unless the benefit to the individual or to society offsets the risk; 2) radiation dosage should be kept as low as reasonably achievable (ALARA); and 3) individual exposure should be subject to dose limits, or to some control of risk in the case of potential exposures.

In addition to these principles, the ACR believes that communicating risk to prospective research subjects should be an integral part of clinical research involving ionizing radiation. The College has incorporated into its relevant ACR Standards that informed consent must be obtained and documented in all elective cases, which includes clinical research. Enclosed are samples of patient consent forms used by the Radiological Diagnostic Oncology Group (RDOG) and the Radiological Therapy Oncology Group (RTOG), as well as examples of how informed consent is incorporated into ACR Standards.

Both the diagnostic and therapeutic research protocols are reviewed three times a year by the ACR's Institutional Review Board (IRB). This panel is composed of nationally renown physicians, ethicists and clergy members. The board's review must first be completed before any clinical studies can begin and before any research institution's respective IRB review of protocols. They conduct a rigorous review process which has been known to disapprove protocols. Moreover, the RTOG maintains a Data Monitoring Committee – again, comprised of physicians, a statistician, and ethicists – which reviews the specific research responses during the conduct of the protocol to assure that proper patient protections are maintained.

Again, thank you for this opportunity to comment. Should you have any questions or need further information, please directly contact Jim Potter at (703) 716-7540.

Sincerely,

John J. Curry
Executive Director

cc: Denise Holmes, ACHRE

APPENDIX A (1/27/95)

RDOG(5) 6881

Stereotactic Fine Needle Aspiration Biopsy and Core Needle Biopsy in the Work-Up of Lesions Detected by Mammography.

Sample Patient Consent Form

RESEARCH STUDY

I have the right to know about the procedures that are used in this clinical study in order to allow me an opportunity to make the decision whether or not to undergo the procedures. This disclosure is not meant to frighten or alarm me; it is simply an effort to make me better informed so I may give or withhold my consent to participate in clinical research.

PURPOSE OF THE STUDY

I understand that the purpose of this research study is to compare the results of needle biopsies to surgical biopsies, or to long term follow-up, for an abnormality found in my breast on my mammogram.

I understand that I will be one of approximately 50-100 women from this institution to be enrolled in this research study. This study is part of a multi-institution project sponsored by the National Cancer Institute. Approximately 3600 women will be enrolled nationwide.

DESCRIPTION OF PROCEDURES

An abnormality has been found on my mammogram (x-ray of my breasts) which has been judged as suspicious for cancer. This abnormality would need further evaluation whether or not I agree to participate in this study.

Ordinarily, breast abnormalities found on mammography are further evaluated in one of three ways: follow-up mammography in 6 months, needle biopsy (breast tissue taken through a needle inserted in my breast), or open surgical biopsy (breast tissue is taken during a surgical procedure). Appropriate further evaluation depends on the way the lesion looks on the mammogram, that is, how suspicious it looks to my radiologist and primary health care provider. I have discussed with my radiologist the option he (or she) would pursue for me if I were not agreeing to participate in this study.

By agreeing to participate in this study, I am consenting to undergo a needle biopsy of my breast (approximately 30-60 minutes). After the needle biopsy, I will undergo either surgery on my breast (approximately 4-5 hours) or follow-up mammography (approximately 15-30 minutes). Whether I undergo surgery or follow-up mammography depends on the result of the needle biopsy and the appearance of the

abnormality on my mammogram. If the abnormality is considered to be highly suspicious by my radiologist, I will undergo surgery regardless of the results of the needle biopsy. If the abnormality is considered to be less suspicious for malignancy by my radiologist and my needle biopsy does not show a cancer, I will undergo follow-up mammography at 6 months, 12 months, and 24 months after my initial mammogram. This will be done to confirm that the lesion is benign. If the needle biopsy shows that I have breast cancer, surgery will be performed to confirm the diagnosis. If the needle biopsy is not useful in making a diagnosis, I will undergo either repeat needle biopsy or open surgical biopsy depending on the judgment of my radiologist and primary health care provider about the usefulness of repeating the needle biopsy.

The needle biopsy itself may be done in several possible ways depending on the study procedure to which I am assigned. This assignment is made not by my radiologist but by a statistical office which will assign the procedure by computer. All patients will undergo needle biopsy with a large needle. At least five samples will be obtained during the procedure. Some patients will be also assigned to undergo biopsies with a smaller needle; this will involve taking additional samples. The main difference between being assigned to the two groups is the number of needle passes. There is no reason to expect that the assignment to either group is more or less advantageous to me. The needle biopsies will be assigned to be obtained by either x-ray or ultrasound guidance.

Estimated Procedure Times:

Mammography - 15-30 minutes
Needle Biopsy - 30-60 minutes
Open Surgical Biopsy - 4-5 hours

In addition, and if available at this center, radiologists will use either ultrasound (images taken by sound waves) or mammography to guide them in making needle passes. The guidance method will be assigned by the statistical office as well. If the guidance method assigned proves ineffective because of either the type of abnormality I have, the location of the abnormality, or the size of my breasts, the radiologist can choose the other guidance method to complete the needle biopsy.

I understand that in undergoing the needle biopsy, the following will occur:

1. X-rays (or ultrasound images) will be taken to localize the abnormality in my breast.

2. I may receive local anesthetic in my breast.

3. If I am assigned to the group requiring small needle biopsy, a fine needle will be placed in my breast in the exact area of the abnormality seen on my mammogram and tissue samples will be taken. My skin will be punctured at least 5 times. **(Institutions planning to use coaxial technique need to rewrite this section to describe the number of fine needle passes they plan).**

4. A large needle will be placed in my breast in the exact area of the abnormality seen on my mammogram and five tissue samples will be removed from different parts of lesion.

5. X-rays (or ultrasound images) will be taken as needed to confirm the correct placement of the needles.

6. If I am going to have a surgical biopsy, a wire will be placed in the area of my breast abnormality to help my surgeon locate it. Additional x-rays will be taken to confirm the correct location of the wire.

RISKS AND DISCOMFORTS

I understand that this study might involve the following risks and/or discomforts:

1. Bleeding, bruising, or infection at the biopsy site.

2. Light-headedness, nausea or vomiting.

3. Allergic reaction to the local anesthetic.

4. Backache.

5. Possible damage to the biopsy site which could make interpretation of the open surgical biopsy material more difficult for the pathologist to interpret.

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CONTACT PERSONS

In the event that injury occurs as a result of this study, treatment will be available. I understand however, I will not be provided with reimbursement for medical care other than what my insurance carrier provide or receive other compensation. For more information concerning the research and research-related risks or injuries, I can notify Dr. _____ the investigator in charge at _____ _____. In addition, I may contact _____ _____ at _____ for information regarding patients' rights in research studies.

BENEFITS

It is not possible to predict whether or not any personal benefit will result from my participation in this study. I understand that the information which is obtained from this study will be used scientifically and possibly be helpful to other women with abnormal mammograms by allowing future patients to have needle biopsies instead of surgical biopsies .

ALTERNATIVES

If I choose not to participate in this study, my care will not be affected. I understand that

I will undergo further evaluation of my breast abnormality as recommended by my radiologist and primary health care provider.

VOLUNTARY PARTICIPATION

Participation in this study is voluntary. No compensation for participation will be given. I understand that I am free to withdraw my consent to participate in this program at any time without prejudice to my subsequent care. I am free to seek care from a physician of my choice at any time. If I do not take part in or withdraw from the study, I will continue to receive care. In the event of a study-related injury, I understand my participation has been voluntary.

CONFIDENTIALITY

I understand that my records will be kept in a confidential form at this institution and also in a computer file at the headquarters of the Radiological Diagnostic Oncology Group (RDOG). The confidentiality of the central computer record is carefully guarded. During their required reviews, representatives of the Food and Drug Administration (FDA), the National Cancer Institute (NCI), or other organizations that have a role in the conduct of this study may have access to medical records which contain my identity. However, no information by which I can be identified will be released or published. Histopathologic material, including tissue on slides or paraffin blocks will be sent to a central pathologist for review.

I have read all of the above, asked questions, received answers concerning areas I did not understand, and willingly give my consent to participate in this program. Upon signing this form I will receive a copy.

_____ _____
Patient Signature (or Legal Representative) Date

_____ _____
Witness Date

APPENDIX I

RTOG 91-04

Phase III Comparison of Accelerated Hyperfractionation vs. Standard Fractionation in Patients with Brain Metastases

Sample Patient Consent Form

RESEARCH STUDY

I, _____, willingly agree to participate in this study which has been explained to me by Dr. _____. This research study is being conducted by the Radiation Therapy Oncology Group and by _____. I understand that while the program will be under supervision of _____. Other professional persons may be designated to assist or act for him.

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PURPOSE OF THE STUDY

I understand fully that my diagnosis is a tumor in the brain which has spread from my previously diagnosed cancer, and that further treatment is recommended. In the past, radiation therapy has been administered in daily doses of 5 days per week for 2 to 4 weeks. Previous research studies have shown that different ways of administering the radiation therapy may produce greater tumor control or relief. One of these ways is the giving of the radiation treatments twice a day. In this study, I agree to receive radiation therapy treatments either once or twice a day. I understand the decision will be made on the basis of computer assignment

This study is part of a National Clinical Trial and I understand that the treatment which offered to me will be based upon a method called randomization. Randomization means that my physician will call a statistical office which will assign one of the two treatments to me and that the chance of receiving one of the two treatments is equal.

DESCRIPTION OF PROCEDURES

The treatment to be given to me is as follows: Treatment One will be radiation treatments given once a day for five days a week for two weeks. Treatment Two will be radiation treatments given twice a day for five days a week for three and half a weeks.

RISKS AND DISCOMFORTS

Cancer treatments often have side effects. The treatment used in this program may cause all, some, or none of the side effects listed. In addition, there is always the risk of very uncommon or previously unknown side effects occurring.

I have been informed of the discomforts and risks which I may reasonably expect as part of the study. Complications due to radiation therapy may include: Hair loss, reddening and tanning of the skin, but might also

result in skin blistering. Other side effects of radiation therapy include possible nausea or headaches, fatigue, and increased sleepiness for several days up to 1-2 weeks, occuring 4-10 weeks after radiation therapy is complete. Cataracts may occur, although every effort will be made to minimize the chance of this occuring. Cataracts can also be caused by one of the medications that is usually used to treat my condition, Dexamethasone (Decadron), a steroid. Irritation of the outer ear canal and/or decreased hearing may occur. There may be some long-term side effects such as poor concentration, poor memory, and poor judgement. There could be a potential risk of eye damage that could lead to blindness.

I understand that there may also be some unknown or unanticipated discomforts or risks in addition to those specified above, but that every precaution will be taken to assure my personal safety and to minimize discomforts.

My physician will be checking me closely to see if any of these side effects are occurring. Routine blood and urine tests and CT/MRI scans will be done to monitor the effects of treatment. Side effects usually disappear after the treatment is stopped. In the meantime, my doctor may prescribe medication to keep these side effects under control. I understand that the use of medication to help control side effects could result in added costs. This institution is not financially responsible for treatments of side effects caused by the study treatment.

CONTACT PERSONS

In the event that injury occurs as a result of this research, treatment for injury will be available. I understand, however, I will not be provided with reimbursement for medical care or receive other compensation. For more information concerning the research and research-related risks or injuries, I can notify Dr._____ the investigator in charge, at_____. In addition, I may contact_____ at _____for information regarding patients' rights in research studies.

BENEFITS

It is not possible to predict whether or not any personal benefit will result from the use of the treatment program. I understand that the information which is obtained from this study may be useful scientifically and possibly helpful to others. The possible benefits of this treatment program are greater shrinkage and control of my tumor and prolongation of my life but I understand this is not guaranteed.

I have been told that should my disease become worse, should side effects become very severe, should new scientific developments occur that indicate the treatment is not in my best interest, or should my physician feel that this treatment is no longer in my best interest, the treatment would be stopped. Further treatment would be discussed.

ALTERNATIVES

Alternatives which could be considered in my case include radiation therapy alone once a day, chemotherapy or surgery which may not necessarily cure me or make my disease less. An additional alternative is no further therapy, which would probably result in continued growth of my tumor. I understand that my doctor can provide detailed information about my disease and the benefits of the various treatments available. I have been told that I should feel free to discuss my disease and my prognosis with the doctor. The physician involved in my care will be available to answer any questions I have concerning this program. In addition, I understand that I am free to ask my physician any questions concerning this program that I wish in the future. I will be provided with a written list of procedures related solely to research which would not otherwise be necessary. These will be explained to me by my physician. Some of these procedures may result in added costs and some of these costs may not be covered by insurance. My doctor will discuss these with me.

VOLUNTARY PARTICIPATION

Participation in this study is voluntary. No compensation for participation will be given. I understand that I am free to withdraw my consent to participate in this treatment program at any time without prejudice to my subsequent care. Refusal to participate will involve no penalty, or loss of benefits. I am free to seek care from a physician of my choice at any time. If I do not take part in or withdraw from the study, I will continue to receive care. In the event of a research-related injury, I understand my participation has been voluntary.

CONFIDENTIALITY

I understand that records of my progress while on the study will be kept in a confidential form at_____ and also in a computer file at headquarters of the Radiation Therapy Oncology Group. The confidentiality of the central computer record is carefully guarded. During their required reviews, representatives of the Food and Drug Administration (FDA), the National Cancer Institute (NCI) and other groups or organizations that have a role in the conduct of this study may have access to medical records which contain my identity. However, no information by which I can be identified will be released or published. Histopathologic material, including slides, may be sent to a central office for review. I have read all of the above, asked questions, received answers concerning areas I did not understand, and willingly give my consent to participate in this program. Upon signing this form I will receive a copy.

_____ _____

Patient Signature (or Legal Representative) Date

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APPENDIX I

RTOG #

TITLE

Sample Patient Consent Form

RESEARCH STUDY

I have the right to know about the procedures that are used in my participation in clinical research so I have an opportunity to decide whether or not to undergo the procedure after knowing the risks and hazards involved. This disclosure is not meant to frighten or alarm me; it is simply an effort to make me better informed so I may give or withhold my consent to participate in clinical research.

PURPOSE OF THE STUDY

It has been explained to me that I have . The purpose of this study is

DESCRIPTION OF PROCEDURES

This study involves at random *(by chance)* assignment to one of two treatment arms. It is not clear at the present time which of the two regimens is better. For this reason the therapy which is to be offered to me will be based upon a the method of selection called randomization. Randomization means that my physician will call a statistical office which will assign me one of the two regimens by computer. The chance of my receiving one of the two therapies is approximately equal. I will be assigned to one of two treatments:

RISKS AND DISCOMFORTS

Cancer treatments often have side effects. The treatment used in this program may cause all, some, or none of the side effects listed. In addition, there is always the risk of very uncommon or previously unknown side effects occurring.

Risks:

My physician will be checking me closely to see if any of these side effects are occurring. Routine blood and urine tests will be done to monitor the effects of treatment. Side effects usually disappear after the treatment is stopped. In the meantime, my doctor may prescribe medication to keep these side effects under control. I understand that the use of medication to help control side effects could result in added costs. This institution is not financially responsible for treatments of side effects caused by the study treatment.

This study may be harmful to an unborn child. There is insufficient medical information to see whether there are significant risks to a fetus carried by a mother who is participating in this study. Therefore, participants who are still menstruating and have not been surgically sterilized must have a negative pregnancy test prior to participating in this study. This requires that blood be drawn by venipuncture within 7 days prior to the study. The results will be made available to the study participant prior to the initiation of this study. There may be laboratory testing and procedures required by this study for research purposes. These additional tests may increase my medical bills although the impact will be dependent on my insurance company.

CONTACT PERSONS

In the event that injury occurs as a result of this research, treatment will be available. I understand, however, I will not be provided with reimbursement for medical care other than what my insurance carrier may provide nor will I receive other compensation. For more information concerning the research and research-related risks or injuries, I can notify Dr. _____ the investigator in charge at _____ _____. In addition, I may contact _____ _____ at _____ for information regarding patients' rights in research studies.

BENEFITS

It is not possible to predict whether or not any personal benefit will result from the treatment program. I understand that the information which is obtained from this study may be used scientifically and possibly be helpful to others. The possible benefits of this treatment program are greater shrinkage and control of my tumor and prolongation of my life but I understand this is not guaranteed.

I have been told that should my disease become worse, should side effects become very severe, should new scientific developments occur that indicate the treatment is not in my best interest, or should my physician feel that this treatment is no longer in my best interest, the treatment would be stopped. Further treatment would be discussed.

ALTERNATIVES

Alternatives which could be considered in my case include either surgical method performed off-study with or without radiation therapy either alone or with chemotherapy or treatments to make me feel better, but not necessarily cure me or make my disease less. An additional alternative is no further therapy, which would probably result in continued growth of my tumor. I understand that my doctor can provide detailed information about my disease and the benefits of the various treatments available. I have been told that I should feel free to discuss my disease and my prognosis with the doctor. The physician involved in my care will be available to answer any questions I have concerning this program. In addition, I understand that I am free to ask my physician any questions concerning this program that I wish in the future.

My physician will explain any procedures related solely to research. Some of these procedures may result in added costs but may be covered by insurance. My doctor will discuss these with me.

VOLUNTARY PARTICIPATION

Participation in this study is voluntary. No compensation for participation will be given. I understand that I am free to withdraw my consent to participate in this treatment program at any time without prejudice to my subsequent care. Refusal to participate will involve no penalty, or loss of benefits. I am free to seek care from a physician of my choice at any time. If I do not take part in or withdraw from the study, I will continue to receive care. In the event of a research-related injury, I understand my participation has been voluntary.

CONFIDENTIALITY

I understand that records of my progress while on the study will be kept in a confidential form at this institution and also in a computer file at the headquarters of the Radiation Therapy Oncology Group *(RTOG)*. The confidentiality of the central computer record is carefully guarded. During their required reviews, representatives of the Food and Drug Administration *(FDA)*, the National Cancer Institute *(NCI)*, qualified representatives of applicable drug manufacturers, and other groups or organizations that have a role in the conduct of this study may have access to medical records which contain my identity. However, no information by which I can be identified will be released or published. Histopathologic material, including tissue and/or slides, may be sent to a central office for review and research investigation associated with this protocol.

I have read all of the above, asked questions, received answers concerning areas I did not understand, and willingly give my consent to participate in this program. Upon signing this form I will receive a copy.

_____ _____

Patient Signature *(or Legal Representative)* Date

RADIATION RESEARCH SOCIETY
2021 SPRING ROAD, SUITE 600 • OAK BROOK, IL 60521 • (708) 571-2881 • (708) 571-7837 FAX

April 6, 1995

Ms. Denise Holmes
Advisory Committee on Human Radiation Experiments
1726 M Street NW, Suite 600
Washington, DC 20036

Dear Ms. Holmes:

We have received Dr. Faden's request for the comments of the Radiation Research Society concerning the calculation of radiation risk, communicating radiation risk to prospective research subjects, and whether or not improvements are needed in current practices and requirements. In response, we offer the following statements:

1. For the calculation of radiation risk, the effective dose should be calculated (NCRP, 1993), and the average value of risk applied (currently 5% per Sv) (NCRP, 1993). In some cases, it may be desirable to use more detailed information on the relationship of risk to sex and age (*cf.* Land and Sinclair, 1991).

2. With regard to the communication of radiation risk to prospective research subjects, some comparisons of dose and/or risk should be offered by the institution responsible for the study (as provided in texts such as NCRP, 1994, or considered in references such as Castronovo, 1993).

3. Annual reviews by institutional review boards (IRBs) of their practices and consent forms should be adequate to ensure that they are up to date. If consent forms and IRB practices are modified to account for the comments listed in statements 1 and 2 above, improvements can be expected to result.

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We hope that these comments will aid you in formulating your recommendations for the design and implementation of current policies and recommendations.

Charles B. Meinhold
President, NCRP
Warren K. Sinclair, Ph.D.
Past-President, NCRP
R.J. Michael Fry, M.D.
Editor-in-Chief, *Radiation Research*
Oddvar F. Nygaard, Ph.D.
Professor of Radiology, Case Western Reserve University
Helen H. Evans, Ph.D.
President, Radiation Research Society

We have also consulted with:

E.W. Webster, M.D., Professor of Radiology, Massachusetts General Hospital

S. James Adelstein, M.D., Professor of Radiology, Harvard Medical School

Herman Suit, M.D., Professor of Radiation Oncology, Massachusetts General Hospital

H. Rodney Withers, M.D., Professor of Radiation Oncology, UCLA Medical Center

References:

NCRP, 1993: "Limitation of Exposure to Ionizing Radiation," National Council on Radiation Protection and Measurements Report No. 116, NCRP, Bethesda, MD.

NCRP, 1994: "Advising the Public about Radiation Emergencies," National Council on Radiation Protection and Measurements Commentary No. 10.

Castranovo, F.P., Jr., 1993. "An Attempt to Standardize the Radiodiagnostic Risk Statement on an Institutional Review Board Consent Form," Investigative Radiology, 28, 533-538.

Land, C.E. and Sinclair, W.K., 1991, "The Relative Contribution of the Different Organ Sites to the Total Cancer Mortality Associated with Low Dose Radiation Exposure," Annals of the ICRP 22, No. 1, pp. 31-57, Pergamon Press, New York.

MAR 21 1995

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Medical Department

Ruth R Faden, PhD MPH
Chair
Advisory Committee on Human Radiation Experiments
1726 M Street, NW
Suite 600
Washington, DC 20036

March 16th, 1995

Dear Dr Faden,

Thank you for your letter of March 7th which I received in the mail today concerning my views on radiation risks to human subjects involved in medical studies. I respond below with a paragraph on each of what I take to be the substantive points in your letter, prefaced with a brief description of our work at the Laboratory.

Brookhaven National Laboratory. Relevant work at the Laboratory falls into two categories: (a) radiotherapy research conducted under Food and Drug Administration (FDA) approved Investigational New Drug Applications (IND's), and (b) administration of tracer amounts of radioactivity for nuclear imaging and physiological research, conducted either with Radioactive Drug Research Committee (RDRC) approval (i.e. CFR 361.1 regulations) or under IND's.

Category (a) comprises clinical trials of boron neutron capture therapy (BNCT) for brain tumors and of radioactive drugs designed to give palliative relief of pain to patients with metastatic bone disease. These studies can clearly be judged on the basis of whether there is a potential benefit to the individual subject which outweighs the potential risk. Ethical issues do not differ from those involving other potential new therapies (e.g. chemotherapy regimes) in patients with fatal cancers.

Category (b) studies conducted in either normal volunteers or non-terminally ill patients involve no direct potential benefit to the subject. They include neutron irradiation followed by whole body counting (to measure body composition of calcium, carbon, nitrogen, etc), and PET scanning after administration of tracer amounts of medical isotopes of very short half-life in order to study human biochemistry, physiology and pharmacology. The whole-body counting experiments are evaluated by the RDRC because they also involve administration of tritiated water. Most of the PET studies are also conducted under RDRC regulations. Some of the PET studies are conducted under physician sponsored IND's, and therefore are approved only by the Human Studies Research Committee (IRB).

Calculating radiation risk. Values for radiation absorbed doses to individual organs are multiplied by appropriate weighting factors and summed to obtain an effective dose. A probability that the administered radioactivity will cause cancer is then calculated by multiplying this effective dose by the risk estimate published by the International Commission on Radiation Protection (ICRP). Where possible, the Laboratory Committees (RDRC and IRB) use radiation absorbed doses from published studies in human subjects (e.g. for F-18 2-deoxy-2-fluoro-D-glucose).

For RDRC studies with novel radioactive drugs, principally carbon-11 (half-life = 20 minutes) labeled compounds, estimates of organ radiation absorbed doses are made on the basis of

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biodistribution studies with rodents, using very conservative assumptions. These values are then used to calculate an effective dose which in turn is used to calculated a probability of causing cancer, as above. Because of the conservative assumptions, we believe that our calculated doses, and therefore the probabilities of causing cancer, are overestimates. Most of our radioactive drugs are used in small numbers of subjects, and it is held to be inappropriate to administer radioactive material to additional subjects simply in order to obtain more precise dose estimates, as long as the doses are known to be within the RDRC limitations.

We are aware that the concept of the effective dose was developed for occupational exposure and that there are many problems in applying it to exposure in medical studies. Nevertheless, it provides the benefit of condensing data into a single number, which is convenient for Consent Forms. My personal view is that ICRP risk estimates, while perhaps appropriate or at least prudent when applied to occupational radiation exposures, in fact greatly overstate the risks because they do not take into account recent developments in our understanding of carcinogenesis. I would be happy to discuss this issue further with you, or other members of your committee, if you feel this is desirable.

Communicating radiation risk to prospective research subjects. Our committees have deliberated at length over how to best express the risk in Consent Forms. Our present description, which has been used with minor variations for about five years, is as follows.

The most important potential side effect of radiation is the induction of cancer. However, no harm in a human individual or in a large population exposed at doses as low as that delivered in this procedure (xxx rem effective dose) has been observed. Thus estimation of the risk of harm can be obtained only by extrapolation from much higher doses. The risk so calculated is small, and would raise the normal risk of lethal cancer, which is 20%, by about xx%. For comparison, the average radiation background in the Long Island area is about 150 mrem/year.

Changes in current practices and requirements. It is my opinion that the present system for evaluating proposed research in humans involving exposure to radiation or administration of radioactive materials works well. While some level of governmental oversight of such studies is clearly appropriate, the present model of review and approval or disapproval by institutional committees acting under FDA regulations is eminently sensible. My experience of serving for over 15 years on RDRC's at three institutions (the University of Wisconsin and the University of Chicago as well as BNL) is that these committees ensure that high quality medical research is done, that human subjects do not receive radiation doses which exceed prescribed limits or which are higher than those necessary to obtain meaningful results, and that the requirements of informed consent are met.

Sincerely,

S John Gatley, PhD
Research Scientist, Medical Department
Chair, RDRC

HEALTH PHYSICS SOCIETY

PRESIDENT-ELECT 1993-1994
PRESIDENT 1994-1995
PAST PRESIDENT 1995-1996
MARVIN GOLDMAN
University of California
Dept. of Radiological Sciences
Davis, CA 95616-8742
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E-mail mgoldman@ucdavis.edu

13 April 1995

Ruth R. Faden, Ph.D.,M.P.H., Chair
Advisory Committee on Human Radiation Experiments
1726 M Street, N.W., Suite 600
Washington, D.C. 20036

Dear Dr. Faden:

This is in response to your letter dated 22 March 1995, postmarked 30 March 1995, which only arrived on April 4th. You requested input from our Health Physics Society on some significant issues, but because of your short deadline, we will regrettably not be able to provide the broader consensus from our Society I had hoped for to present to your Committee. We are at a loss to understand why, if you are at all serious about receiving useful input, we were not provided a more realistic response time. However, last weekend we held our Society's quarterly Executive Committee meeting, and this response represents our collective opinion.

Although we have no specific statement to cover the issue of the public's perception of risk and how to communicate this, it is important to attempt to put the issues of dose and risk into perspective, using common reference points. For example, in communicating risks to prospective research subjects, it is often useful to relate the proposed exposure levels to that of natural background radiation, and to mention the fact that background radiation in the US is variable. Furthermore, no health effects have ever been associated with small multiples of background radiation, i.e., there is no demonstrable risk associated with annual exposures totaling about 0.1-0.2 Gy in a lifetime.

Regarding research subjects in a specific study, we would recommend that a simple but complete explanation of the dose, its distribution and localization in the body and its possible consequences, all be summarized in written form, as is currently the requirement and practice for all "approved" studies using human subjects. Our principal response to your questions relates to this issue. There is widespread absence of a sincere commitment to provide the essential information in non-technical language for the lay person, and in the tongue of the potential subject. Even today, we see repeated failures to accommodate the level of scientific understanding of the potential research subject. Many of the "informed consent" forms are poorly prepared, and even though following the letter of the law, are all but unintelligible to the subject for whom they were prepared.

Added to this is the all-to-frequent lack of understanding of potential radiation issues, including risks, by the investigator who counsels the potential research subject. While clearly an expert on the specifics of a proposed medical study, too often the principal investigator or subject interviewer/recruiter, does not possess adequate training to convincingly explain the radiation aspects of the study in a clear, balanced and understandable fashion to the research subject. These "informed consent" forms need a significant increase in quality control and in peer reviewing by competent radiation protection specialists as well as by educators.

On the issue of the adequacy of current requirements, policies and practices in this country, we feel that presently they are more than adequate, if properly implemented and monitored. The United States has one of the most complete and inclusive set of recommendations and regulations regarding radiation protection of the public, including potential research subjects. Although newer knowledge about the mechanism of action and a fuller understanding of the issues concerning low dose exposures are under continual research scrutiny, it is not likely that significant increases in radiation risk factors will necessitate further restriction in human radiation dose limits. We feel that there is a need for continued scientific research commitment on the part of the government to reduce uncertainties and to use sound and solid science to better adjust existing regulations.

As a result of failures in our educational system, we see an almost universal national ignorance of basic science, including the simplest facts about radiation. Based on ignorance, it is understandable why there is such a distorted perception about radiation and an inability to separate the facts from the fantasies. This is but another example of the current national crisis in research, training and education.

Since our Health Physics Society is not only concerned with radiation research, but is specifically dedicated to radiation protection, we would be pleased to review the draft Committee report or assist in any other way you feel might by useful, even though time is short. We hope that these comments are of interest and we appreciate the opportunity to present them.

Sincerely yours,

Marvin Goldman

Marvin Goldman, Ph.D.
President, Health Physics Society

MAR 20 1995

UNIVERSITY OF WASHINGTON MEDICAL CENTER

DIVISION OF NUCLEAR MEDICINE

Tuesday, March 14, 1995

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Dr. Ruth R. Faden
Advisory Committee on Human Radiation Experiments
1726 M Street, N.W. Suite 600
Washington, D.C. 20036

Dear Dr. Faden

As chairman of the Radiation Safety committee and radiation safety officer of the University of Washington, we would like to share our views on current radiation research issues. The committee reviews over two hundred applications per year from faculty members who propose to use ionizing radiation as part of their studies of human disease. The vast majority of the studies involve the use of X-rays or nuclear medicine studies that would be clinically appropriate for the subjects even if they were not enrolled in the study. Other studies sometimes include normal volunteers as appropriate controls. Some studies propose to use high doses of radiation in developing new treatment protocols for patients with serious life threatening disease such as cancer. None of the studies we have seen over the past 15 years as members of the committee has involved studies of radiation effects on humans. Although such studies were appropriate in the past, and have to be viewed in the context of their time, they are not being done today. At this time, all such studies are done in animals.

In considering a proposal, we look quite carefully at the risks and benefits of the study. Risk is regarded as proportional to radiation dose and we encourage the investigators to minimize the dose when feasible. We are moving toward using the concept of whole body effective dose equivalent to be able to compare the risks of different studies. This is necessary since the risk associated with a dental X-ray cannot be directly compared with whole body exposure of a similar dose. We also consider the expected gain associated with the study. The study should be well designed with sufficient numbers of subjects to be able to draw statistically valid conclusions at the end. The study should be asking a worthwhile question that will result in important new information or new approaches to diagnosing or treating disease. This is obviously a subjective judgement and at times we have difficulty reaching a decision. Whenever we are in doubt, we defer approval and request further information from the investigator.

There are several scientific techniques using low dose radiation that are remarkable effective and accurate approaches to a wide variety of basic and clinically relevant questions. We see the role of committee as insuring that these tools be used in an appropriate and responsible manner. Generally, the risk of injury from radiation is quite low compared to all the other risks in life. However, any unnecessary risk should be avoided if at all possible.

Much of the concern about radiation results from lack of understanding (i.e. fear of the unknown) and because of the way radiation is treated by the media. The public has grown up reading numerous stories, often in comic book format, about how radiation can cause sudden and unpredictable mutation. Although this provides fascinating reading material it is very far from the truth. Radiation, and its biological effects, are now actually understood quite well. There is a small but definable risk of radiation causing cancer in irradiated persons. At sufficiently high doses radiation can be fatal. Overall, at the dose levels most persons experience from background radiation and from medical procedures, the risks are microscopic compared to all the other risks associated with modern life.

The current regulations regarding radiation exposure of the public and of radiation workers are quite conservative. It would actually endanger human health more to institute more stringent criteria by making it impossible to do many very worthwhile research studies. The peer review system (i.e. Human Subjects Committees and Radiation Safety Committees), although not perfect, seems to be the best way to ensure the appropriate use of ionizing radiation in human studies.

Sincerely yours,

Michael M. Graham, Ph.D., M.D.
Chairman of Radiation Safety Committee
Professor of Radiology and Radiation Oncology
Adjunct Professor of Bioengineering, and Medicine

Stanley J. Addison, M.S., C.H.P.
Radiation Safety Officer

The Johns Hopkins University School of Medicine
The Johns Hopkins Hospital

Joint Committee on Clinical Investigation

FAXED 2/24

FEB 28 1995

Please address reply to:
Administration 129 / School of Medicine
720 Rutland Avenue / Baltimore MD 21205-2196

(410) 955-3008
FAX (410) 955-4367

February 24, 1995

Ruth R. Faden, Ph.D., M.P.H.
Chair
Advisory Committee on Human Radiation Experiments
1726 M. Street, N.W., Suite 600
Washington, D.C. 20036

Dear Dr. Faden:

I am responding to your letter of 2/7/95, sent to Ms. Barbara Starklauf. Ms. Starklauf forwarded the letter to me as Chairman of one of the School of Medicine IRBs. I am pleased to have the opportunity to provide comments to the Advisory Committee on the current system for protection of human subjects who participate in research studies.

It is my belief that the current regulations issued by DHHS and FDA provide an adequate basis by which the rights and welfare of human subjects may be safeguarded. This is not to say that there could not be improvements made in the systems by which these regulations are applied or implemented. Nevertheless, the Belmont Report continues to be the penultimate source document outlining the key principles to which researchers should adhere.

I believe, too, that the conduct of local IRB review is the most effective mechanism for ensuring compliance at the level of individual investigators and for determining that consent statements are designed for comprehension by local populations.

With these statements in mind, I would like to suggest that the Commission should acknowledge that it takes an enormous commitment on the part of local institutions to assure that the IRB process works effectively. There is currently no mechanism for DHHS review or site visits of IRB functions to identify procedures or practices which are effective or which should be improved. There is no national educational effort aimed at individual IRBs to encourage not just compliance with the letter of the law by providing paper documentation of processes, but also to address the need to follow the spirit of the laws aimed at protection of human subjects in research.

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Issues surrounding the process of obtaining truly informed consent from subjects remains one which requires constant debate and proposed, workable solutions that can be implemented by local IRBs. Consent forms should not be lengthy, legal documents written to satisfy lawyers. A recent example of the extremes to which consent form writing can be taken is revision to NCI breast cancer treatment protocol consent forms. Currently, some of the consent forms for these trials are 11 pages long. We submit that patient comprehension of research risks and benefits is not augmented by such long complicated forms.

It would be useful to IRBs if there was a direct line by which they could engage in dialogue with federal funding agencies, the DHHS, and the FDA with regard to issues which arise in the formulation of consent documents. Unfortunately, the current mode of operation is for a federal or non-federal sponsor to demand use of proscribed consent documents without any input from local IRBs which understand the population to which the forms will be presented.

You asked specifically for comments about radiation research. It has been the experience at this Institution, which in addition to the IRB has a separate Clinical Radiation Research Committee (CRRC), that investigators are often unaware of the correct method for calculating dose equivalents with regard to radiation exposure and, thus, find it difficult to express radiation risk statements in consent forms. The CRRC has developed worksheets to assist investigators in calculating correct doses for research related radiation exposure and has developed radiation risk statements for consent forms. The ability of subjects to truly understand these statements about radiation risks and to place these risks into perspective is not clear.

The JCCI and the CRRC believe that there is a lack of information on the extent to which human subjects are exposed to radiation related research procedures. Collection of such information in a systematic way would enable one to approach the question of whether changes should be made in the way this type of research is conducted.

Finally, I see a disturbing trend nationally to make IRBs the policy enforcer for institutional policies that are only peripherally involved with human subjects research. I do not believe that IRBs can adequately fulfill their charge of protection of human subjects if they are expected to serve as a policing mechanism. The role of IRBs should be that of determining if there is compliance with human subjects policies. It should be the role of the Institutional administration to determine the actions and sanctions that should accompany any cases of confirmed non-compliance with policies. This is the way that Johns Hopkins operates, and we suggest that it should be the norm.

I hope that my remarks will be useful in the formulation of your recommendations to the Administration.

Sincerely yours,

Thomas R. Hendrix, M.D.
Chairman, JCCI
c/o 129 S/H Admin. Bldg.

TRH:bls
cc: Dr.Michael M.E. Johns
Dr. David A. Blake
Dr. J. James Frost (Chairman, CRRC)
Ms. Barbara L. Starklauf

UNIVERSITY OF MINNESOTA

Twin Cities Campus

Institutional Review Board:
Human Subjects Committee

Suite 10
1300 South Second Street
Minneapolis, MN 55454
612-624-9829
Fax: 612-626-9755

FEB 21 1995

February 15, 1995

Ruth R. Faden, Ph.D., M.P.H.
Chair
Advisory Committee on Human
Radiation Experiments
1726 M Street, N.W., Suite 600
Washington, D.C. 20036

Dear Dr. Faden:

Thank you for your letter of 2-7-95 concerning ethics in radiation research. As an academic nuclear radiologists and an IRB chair, I am particularly interested in your committee's work.

Although I would like to comment specifically on the material that you are reviewing, this will not likely be possible in light of the 2-24-95 deadline.

My general comments are ones that you have no doubt heard repeatedly. The focus of Federal policy on the welfare of subjects should never be compromised by bureaucrats' love of detail and paperwork. That is, keep the system simple, and then local IRBs will be more likely to be successful in the mission of subject protection.

Please contact me if I can be of further assistance.

Sincerely,

Christopher C. Kuni, M.D.

CCK/cz

UNIVERSITY OF CALIFORNIA, BERKELEY

RADIATION SAFETY COMMITTEE &
OFFICE OF RADIATION SAFETY
UNIVERSITY HALL, 3rd FLOOR
BERKELEY, CALIFORNIA 94720

March 18, 1995

Denise Holmes
Ruth R. Faden
Advisory Committee on Human Radiation Experiments
1726 M Street, N.W., Suite 600
Washington, D.C. 20036

RE: Response to Your Request on Human Radiation Experiments

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Dear Ms Holmes and Faden:

We want to thank you for the opportunity to comment on human radiation experiments.

Prior to offering a response to your specific request, we want to share with you our method of assuring that human use of radioactive materials or radiation is done properly.

Informed consent is an essential element of human radiation experiments and an essential element that is the basis of the process described below.

When a researcher first proposes to use radioactive materials or radiation on human subjects, we begin approval via two parallel paths. The researcher submits an application to the Committee for the Protection of Human Subjects (CPHS) and to the Radiation Safety Committee (RSC). The campus Radiation Safety Officer investigates the use, prepares information related to doses and other information, prepares a use authorization or report, and routes these materials for review and/or approval by the

Human Use subcommittee of the RSC and the CPHS. The Human Use Subcommittee of the RSC has essentially the same membership as the RSC with the addition of a board certified Radiologist and/or a medical doctor familiar with radiation issues.

The request is reviewed by the CPHS and the RSC Subcommittee. The RSC Subcommittee provides a report to the RSO and to the Chair of the RSC. Once the Subcommittee, the RSO, and the RSC Chair are satisfied that the use is worthwhile and proper, they verify that the CPHS has completed their evaluation and that they too are ready to approve the use. Once all these are in agreement, the use is submitted for approval to the full RSC. After the RSC approves the use, a request to the California Department of Health Services (Radiologic Health Branch) is made. After the State approves the use, the Office of Radiation Safety prepares a permit that is approved by the user, the department chair, the RSO, and the Chair of the RSC. Periodically during the term of the Radiation Use Authorization, the Office of Radiation Safety surveys the work being performed.

It is our belief this system has so many checks and independent reviews there is little chance for unauthorized or inappropriate use exists. In addition, there is also the control offered by the informed consent process. It is our belief that if others were to use a similar process, complaints about the use of radioactive materials in research would be virtually eliminated. No process can stop intentional or accidental misadministrations. These problems must be handled as appropriate to their cause.

Comments on Your Letter

Again, it needs to be noted that informed consent was, is, and should be an essential element of the human radiation experiments.

The Chair of our Radiation Safety Committee has served as part of the Radiation Safety Committee for 30 years. His close association with the Lawrence Berkeley Lab (LBL) and the University of California San Francisco Medical Center allows for a continuing history of the human use and administration of isotopes such as plutonium. As such, we offer the following for your consideration.

No unauthorized administration of radioactive materials should ever be allowed. The patient must knowledgeably consent to the administration. Consent must be based on a full understanding of the potential effects of the material and the risks associated with the material. The patient needs to signify both that he/she consents and that he/she understands the consent and treatment.

Those who are reviewing administrations of radioactive materials of the forties, fifties and even the sixties need to remember that these materials were not the only ones that were not controlled or administered under the controls that we would all agree are the minimum in the nineties. There needs to be a search to determine who was exposed inappropriately and to determine the dose. However, there also needs to be an understanding of the times in which these events occurred. Few radiation safety professionals we have spoken to believe that these administrations were done with malice or disregard for the welfare of the patient.

Let us learn from these past events and not let them recur.

If I can be of assistance please contact me at (510) 643-7976.

Sincerely,

Paul Lavely for R.W.
Roger Wallace
Chair, Radiation Safety Committee

Paul Lavely
Paul Lavely
Radiation Safety Officer

cc Vice Chancellor J. Cerny

Yale University
The School of Medicine

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February 21, 1995

Ruth R. Faden, Ph.D., M.P.H.
Chair
Advisory Committee on Human Radiation Experiments
1726 M Street, NW, Suite 600
Washington, DC 20036

Attention: Denise Holmes

Dear Dr. Faden: Ruth

I am writing in response to your letter of February 7, 1995. First, I want to thank you for your invitation to share my views on the current system for protection of the rights and interests of research subjects. I believe that, all things considered, the system is working quite well. I am enclosing a copy of a chapter I wrote recently for a book edited by Stephen S. Coughlin and Tom L. Beauchamp. This provides an overview of my perspectives on the system. I offer this for your information as well as that of your colleagues on the Advisory Committee and its staff. It should not become part of the public record without the permission of the editors of the book and, if they consider this necessary, its publisher.

With regard to "radiation research": I am not aware that this field requires any special attention in the development of public policy for the protection of the rights and interests of research subjects. That is to say, I can think of no policy change that should be directed exclusively to research in this field. In my view the American system for protection of the rights and welfare of research subjects "matured" in the early 1980s as the Department of Health and Human Services promulgated regulations based on the recommendations of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (National Commission). In this regard, it is significant that the serious ethical problems recently identified in radiation research are, to the best of my knowledge, all related to activities conducted before the American system for protection of the rights and welfare of research subjects matured. I take this as important circumstantial evidence that the field of radiation research presents no special problems that are not addressed adequately by the present system.

There is one important continuing problem in the field of "radiation research." That is, it is difficult to convey meaningful information to prospective research subjects about the risks of radiation exposure. Further, it is difficult for anybody to assess the risks of low levels of radiation. Further discussion of this problem may be found in reference 1 at pages 59-60. As noted there, we have similar problems with ultrasound, microwaves, electromagnetic energy and other forms of energy exposure.

The remainder of this letter is addressed to your request for my views on what aspects of the current system for protection of rights and interests of research subjects are in need of change.

Firstly, I believe it is essential to decrease the workload of the Institutional Review Board (IRB). The energy of its members is being dissipated in performing tasks that need not be done. I shall offer some specific areas in which the workload might be reduced without risk of diminishing the IRB's effectiveness in performing its important tasks.

With regard to federal grants and contracts, it is now required that all applications be reviewed and approved by the IRB before their submission to the federal government. This means that substantially more than 50% of the protocols reviewed by the IRB will never actually be carried out. (I know that 50% is rather an optimistic estimate of the proportion of applications that get funded. However, a considerable number of those not funded by the federal government are eventually funded by somebody.) Thus, I suggest that changing the system to require IRB review only after funding decisions have been made would greatly reduce the workload of the IRB without allowing any actual performance of research involving human subjects without IRB review.

To further reduce the workload I would authorize expedited review procedures for all amendments to protocols that are submitted within the period of approval for the protocol. I would further authorize the use of expedited review procedures for annual reapprovals. The purpose of such expedited review would be to determine whether it is necessary to submit the amendment or the protocol to the full IRB for review at a convened meeting. Most amendments and most annual reapprovals should not require review by the entire IRB.

Another recommendation to reduce the workload of the IRB is to decrease the necessity for excessive and non-productive paperwork. For example, in recent years IRBs have been deluged with reports of all "adverse drug experiences" that occur anywhere in the world in connection with studies on investigational new drugs. The vast majority of these reports are of incidents that are either completely unrelated to the drug or, if related, they are already well-known and have already been anticipated in the protocols and consent forms. In the past, IRBs would receive these reports along

with some advice from the sponsor regarding the possibility of a causal connection between the drug and the event. Now IRBs almost invariably receive formal disclaimers pointing out that the mere fact of reporting does not constitute an acknowledgement on the part of the sponsor that there is any causal connection between the drug and the adverse event. Moreover, many sponsors require letters of acknowledgement of receipt by the IRB of each adverse experience report. This system could be made very much more efficient. I suggest limiting the reporting requirement to adverse events that are both serious and not anticipated. By "not anticipated" I mean that one of the following two criteria is satisfied. 1) The event is unlike anything described in the protocol or consent form. 2) The event may be like something anticipated in the protocol and consent form but of a much more serious nature than originally anticipated. For example, in the protocol there may be a statement that allergic reactions could occur. The new "unanticipated" event could be that the drug administration was associated with anaphylactic shock.

I believe it is necessary to have a permanent federal advisory body whose sole function is to provide authoritative advice on the ethics of research involving human subjects. I suggest that it should have all of the features that gave a high degree of credibility to the National Commission in the mid-1970s and to the Ethics Advisory Board in the late 1970s. Perhaps the currently proposed National Bioethics Advisory Commission will have such credibility. This advisory body should have a mandate similar to that of the EAB. In general, it should review categories of research rather than specific protocols. Review of specific protocols would be called for in specific categories identified by the National Commission as needing EAB review -- e.g., proposals to conduct research involving children in which more than minor increases above minimal risk are presented by procedures or interventions that do not hold out the prospect of direct benefit.

The federal advisory body should be called upon to review categories of research such as the use of fetal tissue for transplantation purposes, blastomere "biopsies," durable power of attorney for research purposes, and other similar categories of activities that are beyond the scope of the local IRB.

I think it is most unfortunate that DHHS never promulgated regulations in response to the National Commission's recommendations on "those institutionalized as mentally infirm." DHEW did write proposed regulations in response to the National Commission's recommendations. However, they were highly unacceptable in that they were not truly responsive to the National Commission's recommendations. In response to an overwhelmingly negative response from the public, they were withdrawn and no new proposal was ever issued (1, at pp. 269-70; 5).

I believe it is important to review the current federal policy for the protection of the rights and interests of human research subjects with the aim of updating them. It is time to acknowledge the fact that almost all of our regulations reflect an attitude of protectionism. They were written in a time when the prevailing image of research was that it was highly dangerous and characterized by exploitation of vulnerable individuals by socially powerful scientists. The prevailing popular perception has changed. I have written a brief survey and analysis of this change in public perception (2). I believe the time has come to reevaluate and, to some extent, rewrite some of the regulations. Groups of individuals that used to be "protected" by being kept out of research are now protesting that they want to be included. You are, of course, highly familiar with the rightful demands of women to be included as research subjects and the reasons for these demands. There are currently similar activities in various stages of development to facilitate inclusion of other previously excluded groups. One such effort is designed to revise the regulations to permit the enrollment of mature minors in research without permission of their parents or guardians (3). There are also various groups working to revise policies to facilitate access of prisoners to investigational new drugs and to clinical trials (4). The regulations for research involving the fetus also require revision in that they were never "logical" in the first place; owing to a directive from Congress, the National Commission was required to issue its recommendations for research involving the fetus before it had time to accomplish the conceptual clarifications that characterize the remainder of its recommendations (1, at pp. 297-299).

Once again, I thank you for your invitation to share my views on the current system with you and your colleagues. I close by sending my best wishes to you and your colleagues on the Advisory Committee for success in your vitally important project.

Sincerely,

RJL/kp

Robert J. Levine, M.D.

1. Levine, RJ: Ethics and Regulation of Clinical Research. Urban & Schwarzenberg, Baltimore, second edition, 1986.

2. Levine, RJ: The impact of HIV infection on society's perception of clinical trials. Kennedy Institute of Ethics Journal. 4 (No. 2): 93-98, 1994.

3. I am referring to a project undertaken by the Society for Adolescent Medicine (SAM) under the direction of John Santelli, M.D., M.P.H. of Johns Hopkins. They have drafted a set of guidelines for the conduct of research involving adolescents. Among the novel features of these guidelines is the proposal that "mature minors" should be permitted to authorize their own involvement in some types of research without permission of their parents or guardians. Some of the features of this new policy may be found in an earlier proposed policy published by Rogers, AS, D'Angelo, L, and Futterman, D: Guidelines for adolescent participation in research: Current realities and possible resolutions. IRB: A Review of Human Subjects Research. 16 (No. 4): 1-6, July/August 1994. I have a paper in press on this topic: Adolescents as research subjects without permission of their parents or guardians: Ethical considerations. Journal of Adolescent Health. If it would be useful to the Advisory Committee, I could ask Dr. Santelli for permission to send it to you.

4. A currently active project is being conducted by the North Jersey Community Research Initiative (NJCRI) under the direction of Gary Stein, J.D. with funding from AmFAR. An earlier project resulted in a published "overview" paper by Dubler, NN and Sidel, VW: On research on HIV infection and AIDS in correctional institutions. The Milbank Quarterly 67 (No. 2): 171-207, 1989.

5. I am not proposing adoption of the National Commission's recommendations without modification. My proposal is described in a paper based on a talk I presented at the Conference "Ethics in Neurobiological Research with Human Subjects" in Baltimore, January 7-9, 1995. If it would be useful to the Advisory Committee, I could ask the Conference Chairman, Dr. Adil Shamoo, for permission to send it to you.

Enclosure

FEDERAL EXPRESS

THE JOHNS HOPKINS

CENTER FOR CLINICAL TRIALS

Department of Anesthesiology and Critical Care Medicine
Department of Biostatistics
Department of Epidemiology

Department of Medicine
Department of Ophthalmology
Oncology Center

Friday, 24 February 1995

Ruth R. Faden, PhD, MPH, Chair
Advisory Committee on Human Radiation Experiments
1726 M Street NW, Suite 600
Washington, DC 20036
Attention: Denise Holms

Dear Dr. Faden:

I am writing pursuant to your invitation for input to your deliberations as per your mailing of 8 February 1995. I write from the perspective of a researcher with experience in the design and conduct of experiments (primarily clinical trials) involving human beings, and as chair of two IRBs, one here in the School of Hygiene and Public Health and the other at the Maryland Medical Research Institute in Baltimore. I have no first hand experience in radiation research, hence, my comments are of a generic nature relating to research on human beings and to the IRB process regarding the reviews of such research prior to initiation and while underway.

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From the perspective of a researcher trying to do the right thing in regard to persons researched upon there are aspects of the events and political climate leading to your work that are both reassuring and frightening — reassuring in that I believe we need constant vigilance to keep us, individually and collectively, from crossing the line of indiscretion, but frightening because of the rush to indict and impugn an entire research enterprise on the basis of isolated cases. The current atmosphere is frightening, as well, because of the rush to judge by today's norms and standards things done in the past under other norms and standards. I append a copy of written testimony, given to the Committee on Governmental Affairs of the United States Senate, (John Glen, chair; dated 20 January 1994; hearing held 25 January 1994) in relation to hearings stemming from public concern regarding radiation experimentation. That note speaks to the changing view we have had in regard to radiation exposure over the last 40 or 50 years and to the dangers in characterizations of research in emotion laden terms.

My hope is that you and your committee will exercise due caution in formulating recommendations for "fixes". All too often our societal remedies are worse than the condition being remedied. It is unlikely that any "fix", no matter what, will provide an ironclad guarantee of our being free of the risk of abuses of the kind to be prevented.

The system in place, via IRBs, works against such abuses. Imposing other layers of bureaucracy, and reviews on top of that structure, is a course of action to be resisted. The story of the last decade or two has been to increase the level and nature of reviews and controls on clinical research. As a result, such research has become costly to carry out, both in dollars and in time required. The perceived inefficiency has itself been the subject of hearings and enquiry, most recently in regard to the AIDS research effort and in the treatment and prevention of breast cancer. The clinical researcher

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is being squeezed between competing societal forces, one requiring more restraint and caution and the other requiring less caution and greater speed. The FDA, as an embodiment of the clinical research enterprise, has scars from exposure to both forces and most recently from the force urging more speed and less caution. Full page ads appearing in various major newspapers around the country in the last few weeks assert: *If a murderer kills you, it's homicide. If a drunk driver kills you, it's manslaughter. If the FDA kills you, it's just being cautious* (NY Times; FDA becomes target of empowered groups; Philip J Hilts). The concern, given the collective urge to demonstrate that the issues that gave rise to your work will lead to "fixes", is that we will end up with still more constraints and thereby increase the risk of harm to our collective health by lack of resolve, speed, and efficiency in addressing our health concerns and needs.

A trouble plaguing celebrated cases or issues, whether they be of a generic nature, such as yours, or of a more specific nature, as seen most recently in regard to the National Surgical Adjuvant Breast and Bowel Project (NSABP) and fabrication of data, is the tendency to regard isolated events as the rule rather than the exception. In the eyes of the public, we are seen as researchers, so driven by our quest for fame and fortune, capable of any act so long as it advances our cause. We live in an era without need for denominators. Numerator counts are sufficient to reach conclusions and for implementing "fixes". I trust the committee is a respecter of denominator data and that it will base its conclusions and recommended "fixes" on conclusions supported with denominator data.

An option floated in various quarters, to which I confess some instinctive wariness, is a national IRB of sorts. I support the notion that we would benefit from a standing commission akin to that producing the Belmont Report but not the notion of an added layer of review for individual studies. There are already too many layers of review. If we are to move in the direction of a national IRB we should do so with a revamping of the existing IRB structure and review processes. That some revamping is in order is obvious from the time and effort required for initiating any multicenter activity. Every participating site reviews the proposal as if it were the only performing site and does so without regard to reviews of other IRBs, including that of the parent IRB (ie, the one from which the proposal emanates or from which it starts its course through other IRBs). Indeed, from this perspective some process requiring a detailed and searching review at the parent site and with that review recognized by sibling sites would be advantageous. However that could be achieved by streaming existing structures, rather than by adding layers of review to that structure.

The "typical" view of IRBs, from the perspective of individual investigators, is one of mild disdain. At best, one's IRB is viewed as an obstacle to be dealt with rather than being seen as a resource and force for keeping one from doing something that is questionable or wrong. More often than not, suggestions for change emanating from such reviews are seen by investigators as the product of a group of ne'er-do-wells, consummately naive about the realities of research. The committee and its work is neither well understood nor appreciated.

"Fixes" are needed to improve the climate of research institutions in regard to the ethic IRBs are charged with protecting. IRB practices vary in regard to review of the underlying rationale and design for a proposed study. The supposition in the corridors of most research institutions is that IRBs are concerned primarily with consents and the way they are worded. Hence, a challenge to one's work from an IRB, because the underlying rationale is weak or because the design is judged to be inadequate, is likely to be seen as idle meddling. The hand of IRBs should be strengthened by making it clear to all concerned that they are obliged to reject research having faulty rationale or

design, even if it is considered to be harmless. One can reasonably argue that research so poorly conceived, designed, or conducted so as to be worthless is, by definition, unethical because it has no benefit to those being researched upon and, hence, even the mere nuisance of being contacted, let alone attendant risk if any, is unjustified.

Given my druthers, I would be moving toward a form of certification for researchers as a condition for conducting research on human beings. The institution would be responsible for certification and the individual would be responsible for maintaining the certification. The certification would consist of exposure, in didactic settings, to the norms and standards for research on human beings and would include review of existing principles of medical ethics, starting with the Nuremberg Code and its precursors. Included as well would be discussions of the nature and function of IRBs and IRB-investigator commitments and expectations. The concept of certification would be extended to administrative heads of departments and institutions, including chairs, deans, presidents, and CEOs, regardless of whether or not they themselves are ever to submit a research proposal for IRB review.

Another change in relation to IRBs would be to strengthen their hands in requiring forms of ongoing monitoring in relation to studies where continuation depends on a sustained state of equipoise. The issue of prudent continuation arises principally in randomized trials and in other ongoing activities affected by changes in our state of knowledge. IRBs are largely indifferent to issues of ongoing monitoring in relation to sustained states of equipoise. Most major journals require evidence of IRB review and of informed voluntary consent on the part of those being studied, as a condition for publication, but are indifferent to whether or not investigators performed interim analyses to allow them to alter the study design or terminate the study if indicated by accumulated data. Indeed the Tuskegee Study is, in effect, a study without such monitoring.

Preoccupation with p-values and statistical significance, and confusion regarding interim looks at data, has resulted in a clinical enterprise in a collective lethargic state in regard to the need for ongoing monitoring. Trials justified at the outset — there being a state of equipoise regarding the treatment regimens to be tested — are appropriately continued only so long as that state remains. Continued enrollment and treatment, once a trial is underway, is justified only so long as a reasonable state of equipoise remains. It can be argued that one is obligated to stop enrolling or treating and to modify the design or stop the trial when the data from the trial or elsewhere indicate that the state no longer prevails.

Investigators are encouraged to avoid peeks at their data over the course of a trial, if for no reason other than fear of criticism from their peers when their work is published. Drug companies resist the notion of interim looks for fear that such looks will cause the FDA to question their findings when and if the trial is used in relation to a new drug application. Indeed, the FDA sends out mixed signals regarding the need for interim looks. To be sure, it encourages such monitoring on principle, and now especially in the wake of the recent tragedy regarding a drug with promise for treatment of chronic hepatitis virus B (FIAU), but at the level of individual review officers, the FDA remains more comfortable with data from trials being run to their appointed ends devoid of peeks than with trials with peeks for ongoing monitoring.

Any study where continuation depends on a sustained state of equipoise should be required to have ongoing monitoring as a condition for approval. Implicit in that requirement is the establishment and

maintenance of real time data flows so that meaningful analyses can be performed. Trials involving the case report form of data collection (ie, where the entire set of forms needed for enrollment and followup of a patient is completed before the set is sent to the data processing center) would be considered to violate the real time data flow requirement, absent other "workarounds". The monitoring requirement should apply to single center as well as multicenter studies and should, typically, be performed by some person or body (committee or board) independent of the research. Unless the investigator can mount compelling arguments as to why such monitoring is not needed (in that its absence poses no threat to patients), it should be required.

A "fix" that truly has been needed for some time, is a system of registration of all studies involving research on human beings. I argue that being able to carry out research on human beings is a privilege, not a right, and that being able to do so is a form of public trust regardless of who supports that research; that violations of procedures, norms, or standards serve to erode that trust, individually and collectively. I reject the notion of confidentiality or "secrecy" in all forms of research involving human beings because of its inherent and obvious dangers. I believe that any research proposal, once approved, should be a matter of public record. That record should include details regarding the rationale of the study and about its design and protocol. I believe, as well, that academic and governmental funded institutions should, on principle, refuse funding requiring those who perform the research to be constrained from making basic information, such as that listed above, available. I believe also that the product of IRBs, in the form of approved proposals, should automatically become part of a national archive as produced via harvests from local IRBs. A central registry, so produced and maintained, would have obvious advantages. Were such a registry to have been in place years ago we could have been spared much of the rhetoric regarding gender bias (ie, as to whether or not it exists in trials and in other areas of the clinical research) and would have a better basis for investigations of the kind you are doing. It is puzzling why we, as a Nation, have found it easier to curse the darkness rather than light a candle in this regard. Perhaps your work at least will cause us to strike a match.

Sincerely,

Curtis L Meinert, PhD
Professor

CLM/klc

Enclosure
Copy of written testimony presented to Committee on Governmental Affairs of the United States Senate (25 January 1994)

Distribution
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10:32am (Fri) 24 Feb 95

Committee on Governmental Affairs of the US Senate

Hearing on radiation and other experimentation on human being
20 January 1994

Testimony of Curtis L Meinert

Curtis L Meinert, PhD
The Johns Hopkins University
School of Hygiene and Public Health
Department of Epidemiology
Professor of Epidemiology and Biostatistics

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Senator Glenn, Committee members, I am pleased to have the opportunity to comment on the issues being addressed in these hearings. My area of expertise is as a methodologist trained in the fields of biostatistics and epidemiology, with a specialty in the design and conduct of clinical trials. I am the founding editor of *Controlled Clinical Trials* and the author of a textbook having to do with the design, conduct, and analysis of clinical trials. I have served on various IRBs and currently chair the IRB of the School of Hygiene and Public Health of The Johns Hopkins University. I am not a radiation expert nor do I have any experience in radiation studies, hence, I am not in a position to offer opinions as to the legitimacy of the radiation research in question, or on the adequacy of the consent processes underlying those efforts. I wish, instead, to address some of the broader issues being addressed in these hearings. I will start with some general cautionary notes, then proceed to a review of some of the history underlying our research ethics on human beings, then to a review of existing safeguards. I will conclude by offering a few suggestions as to added safeguards.

Personal perspective

My perspective is that of a public health clinical researcher concerned with improving our collective health and well-being by trying to make certain the treatments that we use are safe and effective. The primary tool for such evaluations is the randomized clinical trial. The sad fact is that most of the treatments in use today have not been adequately tested using that tool. Equally sad is the fact that when we do test some of our supposedly tried and true treatments via randomized trials they are found to be of questionable value.

On the difference between that which is ill-advised vs that which is unethical

We need to distinguish between that which, in retrospect, is judged to have been ill-advised as opposed to that which was unethical by the standards of the time. As suggested, many of the treatments and remedies in use today will be judged as useless or ill-advised at some time in the future. This is easily seen when one looks back in time. The account of Ambroise Paré, a surgeon in the battle to capture the castle of Vilaine in 1537, serves as a graphic reminder of this fact. The treatment for gunshot wounds in those days consisted of dousing the wound with boiling oil. Fortunately for those wounded, the battle was so heated so as to cause Paré to run out of boiling oil and causing him to use an ointment made of egg yolks, oil of roses, and turpentine instead. To his great surprise he found, on visiting his patients the following morning, that those treated with the ointment fared better than those treated with the boiling oil. He wrote:

> *I raised myself very early to visit them, when beyond my hope I found those to whom I had applied the digestive medicament, feeling but little pain, their wounds neither swollen nor inflamed, and having slept through the night. The others to whom I had applied the boiling oil were feverish with much pain and swelling about their wounds. Then I determined never again to burn thus so cruelly the poor wounded by Arquebuses.* (Packard FR, *Life and Times of Ambroise Paré, 1510 - 1590*, Paul B Hoeber, New York, 1921)

Whenever I tell students this story, in a course I teach on trials, I see smiles of bemusement at the apparent stupidity of Paré, until, that is, I remind them that others will stand where I stand years hence telling similarly "amusing" stories about our treatments. The point of the story is that norms for what is ill-advised change with time, and had Paré

had the wherewithal and wisdom to test his preferred treatment he could have spared his patients an unpleasant and ineffective treatment.

Risk-benefit

There is no such thing as a safe treatment. They all have risks. The best one can hope is that the benefits, on average, outweigh the risks. There is, I fear, a collective naivety in the public regarding the so called risk-benefit ratio of treatments. We want the benefits but none of the risks, and we are always surprised when we discover that a seemingly safe treatment has risks.

The recent flurry of events, and accompanying publicity, regarding radiation studies done in the past has created a crisis of confidence that extends far beyond the specifics of radiation research. It is a crisis that concerns us all whatever our perspective — that of a research subject, a researcher, citizen, or human being. Hence, it is appropriate to have a public airing of the specifics, and of the general issues involved, to restore the trust of the public in the collective research enterprise where indicated, and to correct deficiencies where noted. We will not help anyone, starting with those we try to treat, if this debate leads the public to believe that they are likely to be unwitting guinea pigs every time they enter a health care facility. We have a crisis of confidence that, unless dealt with forthrightly and resolutely, will affect us all, to the extent that we depend on mutual trust and respect in carrying out any research on human beings. The ability to do such work is, itself, a form of public trust and violations of that trust have the potential of pushing us back to the era nonexperimental empiricism in choosing the treatments we use. Even the term guinea pig is unfortunate because of its emotional connotations and because of the implication that lack of experimentation is the preferred state. One can argue, in a broad sense, that all of Paré's patients were guinea pigs in that he used treatments without any convincing data to indicate their effectiveness.

Changing attitudes regarding risks

We also need to remember that our attitudes regarding risk change with time. That which we regard as risky today may have been viewed as innocuous in the past. We need only think of smoking to be reminded of that. Though smoking was not necessarily endorsed by the medical profession, there was no organized objection to advertising claims that more doctors smoked Camels than any other brand. By the same token, there is, I am sure, a goodly number of people in this room old enough to remember wiggling their toes under x-ray machines in shoe stores. The almost ubiquitous nature of those machines tells us something about our attitude regarding radiation at that time.

For all of these reasons, it is unfair and dangerous to use 1994 standards to evaluate processes and practices in the 1940s, 50s, and 60s. Though the interval of time since the 1940's is small measured against the interval since Paré's time, it spans different eras in relation to norms and standards underpinning the research and consent processes.

On the interpretation of numerator data and the absence of information

A disconcerting aspect of revelations of the sort now in the news is that the public is left without any means of knowing the nature or extent of concerns being expressed. The tendency to concentrate on numerator data (counts of questionable studies) without denominator data (counts of all studies) has the real potential for misleading and misinforming. It has the potential of leaving the public with the impression that the system is profoundly flawed, when in fact it is in all probability 99 1/100th % pure.

I urge you, as you proceed with your work, to have the eyes of an analyst. Require denominators for numerator counts. I urge, as well, a healthy skepticism whenever examples are given as proofs for the general claims, especially in relation to such issues as vulnerability of those studied or their demographic mix. All study populations are, in one sense or another, select and, hence, unrepresentative of the population as a whole. Also we need to refrain from assuming that the absence of a documented consent means that consent was not obtained or given.

Consent practices and ethical principles

Practices in place today are the product of an ever changing set of norms and standards. Key documents in this evolution include:

- The Nuremberg Code of 1947
- The Helsinki Declaration of 1964 (subsequent revisions)
- USPHS Surgeon General's memo of 8 February 1966
- The Tuskegee Syphilis Study Ad Hoc Advisory Panel Report (1973)
- The Belmont Report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, entitled *Ethical Principles and Guidelines for the Protection of Human Subjects of Research*, dated 18 April 1979
- The NIH Revitalization Act of 1993

The Nuremberg Code on consent

The Nuremberg Code of 1947 is explicit on the need for voluntary consent, free of coercion, as an essential prerequisite to undertaking any research involving human beings. It reads, in part:

The voluntary consent of the human subject is absolutely essential.

This means that the person involved should have legal capacity to give consent; should be situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, overreaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision. This latter element requires that before the acceptance of an affirmative decision by the experimental subject there should be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonably to be expected; and the effects upon his health or person which may possibly come from his participation in the experiment. (Levine RJ, *Ethics and Regulations of Clinical Research*, Urban and Schwarzenberg, Baltimore, 1981)

USPHS Surgeon General's memo of 1966

Abuses brought to light in the early and mid 60s (involving the use of vulnerable and disadvantaged subjects without their consent) led to the imposition of formal requirements for consents, as well as for documentation of those consents, as a condition for receipt of funds from the USPHS. That led, ultimately, to the current structure and review processes vested in what today are known as Institutional Review Boards (IRBs).

Tuskegee Syphilis Study Ad Hoc Advisory Report

The report of the Tuskegee Syphilis Study Ad Hoc Advisory Panel of 1973 dealt with ethical issues raised in a syphilis study of mostly poor black males living in Macon County, Alabama. The primary issue had to with the failure to offer appropriate treatment to members of the study cohort once an effective treatment (penicillin) became available.

Belmont Report of 1979

The Belmont Report is of note because it served to set forth three basic ethical principles for research on human beings. Those principles are known as the principles of beneficence, justice, and respect for persons.

principle of beneficence: Asserts that the options available to the researcher in treating or caring for persons in a study is limited to that set justifiable and considered to represent beneficent forms of care and treatment

principle of justice: A principle that asserts that the care and treatment performed or offered in a research setting involving human beings must be done in a just fashion; not to the benefit of a few and to the exclusion of others

principle of respect for persons: A principle that asserts that the care and treatment performed or offered in a research setting involving human beings must be done in a fashion denoting respect for those so cared for or treated

1993 NIH Revitalization Act

The portion of the 1993 NIH Revitalization Act dealing with trials has the effect of imposing design standards in an effort to ensure valid analyses for treatment by sex and treatment by ethnic origin interactions, that is, analyses aimed at determining whether the treatments being tested work differently in women than in men or in ethnic minorities than in ethnic majorities. The provision reads in part:

In the case of any clinical trial in which women or members of minority groups will under subsection (a) be included as subjects, the Director of the NIH shall ensure that the trial is designed and carried out in a manner sufficient to provide for a valid analysis of whether the variables being studied in the trial affect women or members of minority groups, as the case may be, differently than other subjects in the trial.

Institutional Review Boards and their function

One of the questions being addressed by the Committee has to do with human experimentation in general, and whether research underway today is being conducted according to the highest ethical, scientific, and medical standards. There is, of course, no way to answer that question with 100% assurance, absent extensive efforts. Even then, those assurances may be called into question years later under a changed value system and new perspectives. Further, in so vast an enterprise, the issue is not whether all that which is underway meets those standards, but rather whether there is anything more that we could or should do to increase our level of assurance. Here I would urge caution and conservatism in proposing new safeguards without convincing evidence of their necessity, and especially without the analogy to an environmental impact assessment as to the effect of new requirements on the research enterprise. As a case in point, the "valid analysis requirement" contained in the NIH Revitalization Act of 1993, taken at its face value, is

likely either to increase the cost of trials without a corresponding return on investment or to reduce the number of trials that can be done on anyone.

Virtually all research involving human beings today is subject to review and approval by IRBs, as constituted and operated under guidelines promulgated by the Office for Protection from Research Risks of the NIH, prior to initiation. Technically, the Code of Federal Regulations (45 CFR §46.111(a)(1)) mandating such reviews and approvals as a condition for initiation applies only to federally funded research, but the usual practice of most research facilities is to require such reviews and approvals regardless of funding source. In addition, changes or modifications following approval are subject to review and approval prior to implementation. Investigators are obligated to report any proposed change in protocol, including those related to enrollment, eligibility, and consent before they may be implemented. The usual practice is to grant approvals for a period of one year at a time. Projects approved may be stopped by the IRB at any time if, in its collective judgment, the project is considered to be unsound or to have violated basic principles set forth in the Belmont Report.

'Research' is broadly defined as:

systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. Activities which meet this definition constitute research for purposes of this policy, whether or not they are conducted or supported under a program which is considered research for other purposes. For example, some demonstration and service programs may include research activities. (45 CFR §46.102(d); 18 June 1991)

The definition includes all research done on or relating to people or their body fluids or tissues, as well as that done on records or data collected on human beings, even if the specific project in question does not involve any contact with persons to whom the records or data pertain.

The regulations set standards for membership and composition of the Boards and specify provisions for protection from conflicts of interest. Specifically, 45 CFR §46.107 states:

(a) Each IRB shall have at least five members, with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution. The IRB shall be sufficiently qualified through the experience and expertise of its members, and the diversity of the members, including consideration of race, gender, and cultural backgrounds and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects. In addition to possessing the professional competence necessary to review specific research activities, the IRB shall be able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice. The IRB shall therefore include persons knowledgeable in these areas. If an IRB regularly reviews research that involves a vulnerable category of subjects, such as children, prisoners, pregnant women, or handicapped or mentally disabled persons, consideration shall be given to the inclusion of one or more individuals who are knowledgeable about and experienced in working with these subjects.

(b) Every nondiscriminatory effort will be made to ensure that no IRB consists entirely of men or entirely of women, including the institution's consideration of qualified persons of both sexes, so long as no selection is made to the IRB on the basis of gender. No IRB may consist entirely of members of one profession.

(c) Each IRB shall include at least one member whose primary concerns are in scientific areas and at least one member whose primary concerns are in nonscientific areas.

(d) Each IRB shall include at least one member who is not otherwise affiliated with the institution and who is not part of the immediate family of a person who is affiliated with the institution.

(e) No IRB may have a member participate in the IRB's initial or continuing review of any project in which the member has a conflicting interest, except to provide information requested by the IRB.

(f) An IRB may, in its discretion, invite individuals with competence in special areas to assist in the review of issues which require expertise beyond or in addition to that available on the IRB. These individuals may not vote with the IRB.

The reviews involve assessments aimed at ensuring that risks to subjects are minimized and that the potential for benefit is greater than the potential for risk. IRBs are obligated to make certain that risks have been minimized before approving any project. The regulations specify that (CFR §46.111(a)(1)):

Risks to subjects are minimized: (i) by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subject for diagnostic or treatment purposes.

Those requirements are taken to imply that research so poorly designed or conducted so as to be worthless is, by definition, unethical because, even if risk free, the nuisance of being studied is not worth the return to the subject.

The nature of the consent required and the kinds of information to be imparted before asking for consent are also explicitly set forth in CFR §46.116(a). The basic elements of consent include the following:

(1) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental

(2) A description of any reasonably foreseeable risks or discomforts to the subject

(3) A description of any benefits to the subject or to others which may reasonably be expected from the research

(4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject

(5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained

(6) For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained

(7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject

(8) A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled

There is, of course, no guarantee that every research project involving human beings is submitted for IRB approval. However, the chances of serious breaches in the IRB approval process are small, if for no other reason than that investigators know they face severe penalties for violations of that process — penalties that include censure, debarment, and dismissal. The chances of serious breaches are diminishingly small in the case of funded research involving human beings, and particularly so in the case of such research involving Federal funds. Institutions receiving such funds are required to certify that IRB approval has been granted prior to release of those funds for use in the research proposed.

Suggestions

Now as to future direction, and whether or not added safeguards are necessary. We have a tendency to intervene and "fix" without any certainty that a fix is needed, and often without much appreciation of the long term implications of the "fix". Common sense dictates the need for a certain conservatism in terms of interventions. The existing IRB process is arduous and sound. Hence, efforts, in my judgment, should go to fine tuning that process rather than imposing still other reviews on top of those already in place. As it stands now, it can take months to obtain the various reviews and approvals needed to proceed. Added levels of reviews will add to that time. As a Nation, we cannot ask the research enterprise to be more expeditious and efficient in developing new treatments for conditions, such as AIDS, on the one hand, and on the other slow it down with added reviews and clearances before projects can be started.

The emphasis should go to providing training for IRBs, and their memberships, in the nature and extent of their responsibilities. Similarly investigators preparing to undertake research on human beings should be required to demonstrate an adequate working knowledge of the norms and ethical principles of research in general, and those pertaining to research on human beings in particular. Federal guidelines now in place mandate such training for the principal investigators (PIs) of training grants as well as all student recipients of funds from such grants (*NIH Guide*; Vol 20, No 32, 23 August 1991). The same kind of training should extend to all personnel preparing to engage in research on human beings.

Projects, once approved, should undergo periodic reviews similar to those performed when the project is first reviewed and approved. Those reviews would be, of necessity, more searching and demanding than the annual reviews now in place. These more extensive reviews might be required every 5 years and would be equivalent, in nature and extent, to the initial review.

Our best defense against abuses is via openness and accountability at the level of individual IRBs, as well as on a collective National basis. There is no way to dispel or combat perceptions, whatever they may be, without data. The fact that we have no organized system for characterizing the nature of our research enterprise works to the disadvantage of all. The "valid analysis requirement" of the NIH Revitalization Act of 1993 arises in large measure from the perception that the collective research enterprise of the Nation is less concerned with the diseases and conditions afflicting women than those of men, and less concerned with the diseases and conditions of the ethnic minorities of our population than those of our ethnic majorities. Though there are reasons to question those perceptions and the usefulness of the valid analysis clause of the Act (*Controlled Clinical Trials*, Vol 14, Dec 1993), such questioning is largely futile without an extensive database enabling us to judge the way in which our resources are spent in researching the various segments of our population.

I urge that consideration be given to implementing a Nationwide system of registration for all IRB approved projects, starting with multiple project assurance (MPA) IRBs. A system of registration at the local IRB level, and a central system for harvesting that information, would give us the means for answering questions such as those raised by Senator Glenn in his letter to panelists. It would have a number of other values as well; for instance, in relation to addressing concerns of equity in regard to our collective research agenda as it pertains to issues of gender and ethnic origin. In addition, it would provide the research community with a means of reducing redundant research and for encouraging collaboration and interaction across institutions.

My hope is that such a system will come into being in my lifetime. I believe we need it.

Thank you.

Mr Chairman, I would be pleased to have the full text of my remarks entered into the Record.

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David D. Oakes, M.D., FACS
Associate Professor of Surgery

February 22, 1995

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Ruth R. Faden, Ph.D., M.P.H.
Chair, Advisory Committee on
Human Radiation Experiments
1726 M Street, N.W., Suite 600
Washington, D.C. 20036

Dear Dr. Faden:

In Dr. James Theodore's absence, I am writing on behalf of Stanford University's IRB in response to your letter of February 7, 1995.

You ask which aspects of the current system for protection of rights and interests of research subjects "are in need of change" and what we would do differently if "charged with the responsibility of ensuring the rights and interests of human subjects in medical research."

The work of your Committee will not be complete without a thorough and detailed review and re-examination of current federal regulations on this topic, as interpreted and administered by the Food and Drug Administration (FDA) and the Office for Protection from Research Risks (OPRR).

Stanford processes a large number of research protocols each year (2500 -3000). Over the years we have developed an elaborate review system that provides a high degree of protection for our research subjects and more than meets regulatory requirements. In 1989 our system was explained in detail and accepted by both FDA and OPRR. It has served our human subjects and our institution well. It could serve as a model for other institutions.

Last year, for no apparent reason, the FDA arbitrarily changed its position and decided that we were not in compliance with their regulations. The procedural changes they have asked us to make seriously impair the ability of large institutions such as ours to guarantee the protection of research subjects.

If your Committee is seriously committed to assuring meaningful institutional review of research protocols for safety and ethical conduct, Stanford would be glad to explain our concerns in detail at a time and place of mutual convenience. I am enclosing a document to provide background on the concerns.

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Please let me know if I can be of further assistance in this matter.

Sincerely,

David D. Oakes, M.D., F.A.C.S.
Associate Professor of Surgery
Stanford University School of Medicine
Former Chairman and Special Advisor to the
Administrative Panel on Human Subjects and Medical Research
Stanford University

DDO:es

Attach: Feb. 12, 1995 memorandum

STANFORD UNIVERSITY SCHOOL OF MEDICINE
MEMORANDUM

February 12, 1995

TO: H. Craig Heller, Ph.D.
Associate Dean of Research

FROM: David D. Oakes, M.D., Associate Professor of Surgery
Stanford University School of Medicine

The following paragraphs represent thoughts on the recent FDA challenge to Stanford's procedures for reviewing medical research involving human subjects. Our current system is so obviously superior to the alternatives that the University almost has a moral obligation to defend our system as vigorously as possible within the government administrative hierachy and possibly in the political arena as well. The following are some basic thoughts which could be expanded or clarified if you see fit.

828

* * *

Following a routine inspection last year (April 26 - May 3, 1994), the Food and Drug Administration (FDA) informed President Gerhard Casper that Stanford's Institutional Review Board "has not complied with FDA regulations" - primarily because every research protocol involving human subjects is not individually discussed at a convened meeting. This sudden change in FDA policy was unexpected, unexplained, and - in our opinion - unjustified.

By way of background, a similar concern was raised by the FDA after its previous routine inspection (March 22 - 24, 1989). At that time we explained that Stanford's procedure relies primarily upon extensive, in-depth review prior to the monthly meetings - by three times as many reviewers as required by FDA regulations. Written questions and answers are exchanged between the reviewers and the investigators and are circulated to all reviewers. This well-documented exchange continues until all the reviewers (a majority of the Committee) are satisfied and have given written approval. Formal approval is still not granted until a convened meeting, at which time any member can raise questions about any protocol on the list of those endorsed by the primary in-depth reviewers. This list is then approved by a block vote without individual discussion unless specifically requested.

In October, 1989, after reviewing the detailed explanation of our process, the FDA informed us that our review procedures "do meet FDA requirements". Our procedure was also explained to and accepted by the Office for Protection From Research Risks which approved our request for a Multiple Project Assurance for calendar years 1991 through 1995. APPARENTLY THE INDIVIDUALS CONDUCTING THE 1994 FDA INSPECTION WERE NOT AWARE OF THE 1989 CORRESPONDENCE ON THIS MATTER. HAD THEY BEEN, THEY WOULD HAVE HAD NO REASON TO REVISIT THIS ISSUE.

Our review process has not changed since 1989.

Federal Regulations have not changed since 1989.

We are not aware of any subject who has been harmed by any perceived deficiency in our review procedures.

We are therefore, justifiably puzzled by being suddenly deemed out of compliance with FDA regulations.

* * *

Stanford's review procedures have evolved over the years as a way of insuring rigorous in-depth well-documented review of research protocols - both to protect human subjects and to fulfill the letter and the spirit of relevant government regulations. As a leading center of biomedical research, Stanford's IRB is asked to review a large number of protocols (presently between 2500 and 3000 per year). Given this volume, we feel that it is neither necessary nor desirable to discuss every protocol individually at a convened meeting.

The advantages of our present system are

1. Reviewers have unlimited time - working individually - to peruse and ponder protocols.

2. Reviewers are forced to focus their concerns into precisely stated questions that are transmitted anonymously to the investigators.

3. The investigators are forced to respond clearly and completely to the specific questions posed by the reviewers. Failure to do so will lead to a further round of correspondence.

4. All reviewers are aware of the questions and concerns raised by the other reviewers. Even if a reviewer initially had no questions, he may be stimulated by another reviewer's questions to raise additional inquiries of his own.

5. Reviewers have an entire month to think and rethink their evaluations and to pose additional questions.

6. All of this interchange is in writing, therefore well-documented and available for future reference and audit. There is little room for ambiguity about what issues were discussed and how they were resolved.

7. By limiting scheduled meeting commitments to a single monthly meeting lasting only one and a half to two hours, it is possible to have one large committee. This permits:

   a) The recruitment and retention of a wide variety (but relatively small number) of experienced, interested, knowledgeable, conscientious reviewers.

   b) The assignment of thrice the required number of reviewers to each protocol.

   c) A high degree of consistency in the standards applied to all research protocols throughout the university.

8. Because full committee discussion is limited to those protocols about which one or more in-depth reviewer raised substantive questions or concerns, discussion time is focused on significant problems rather than wasted on the rote recitation of protocols already approved by a majority of the Committee following in-depth written review. Time is therefore available to discuss broader policy issues of general concern regarding ethical and procedural matters.

By contrast, requiring a detailed discussion of each protocol at a convened meeting is impractical, inefficient, and has numerous disadvantages which quite likely would make it <u>less effective</u> and <u>less reliable</u> in protecting human research subjects at our institution:

1. Even a cursory discussion of a protocol and its consent form could hardly be done in less than 15 minutes. A monthly agenda of even 240 protocols would therefore require 60 hours of meeting time! This would obviously necessitate the formation of multiple committees.

2. Multiple committees would need to be smaller - thus providing fewer reviewers and potentially less adequate review. [Federal regulations require only 5 members for an IRB. A convened meeting requires a quorum (3 members). Approval is by majority vote (2 members)]. Obviously review would be less extensive than under our present system.

3. Multiple committees would require recruitment of many more reviewers - undoubtedly diluting the quality of individuals available to serve in this important capacity.

4. Reviewers would have only one time to raise their questions and concerns - and would do so without communicating with the investigators. Follow-up questions or clarifications would require delay of approval until a second meeting - effectively doubling the work load.

5. Unless a stenographer were present, minutes of the meetings would likely be incomplete and documentation of questions and concerns less satisfactory than our present system.

6. There would likely be variation in the quality and consistency of review performed by a variety of small committees.

7. Financial cost for supplies and administrative support staff would be increased many fold. This, obviously, would be justified if the quality of our review process were improved - but for the reasons discussed above we strongly doubt that this would be the case. Quite the contrary, we feel that we would be <u>less able</u> to assure protection of our subjects from research risks.

It is ironic that the NIH has recently criticized the University of California Los Angeles for "failure by the UCLA Medical Center IRB to require satisfactory written informed consent documents" for two research projects in which participants were allegedly exposed to significant risks about which they had not been adequately warned. On page 22 of the document entitled "Evaluation of Human Subject Protection in Schizophrenia Research Conducted by the University of California Los Angeles" issued May 11, 1994, the Office for Protection from Research Risks, Division of Human Subjects Protection, states:

> "...the UCLA Medical Center IRB is responsible for the initial and continuing review of a very large number of protocols. OPRR invites UCLA to examine whether the creation of additional IRB's <u>or other innovations</u> (emphasis added) might be desirable to enhance UCLA's institutional protections for human subjects."

We respectfully suggest that Stanford's system of premeeting in-depth written well-documented review is just such an "innovation" which provides an effective and efficient way for a large research institution to provide reliable review of a large number of research protocols. We feel that this procedure would "enhance...institutional protections for human subjects" even for smaller IRB's.

We should not only vigorously defend our system, we should also commend it to others.

I would be delighted to discuss any or all of these issues with you at your convenience.

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February 22, 1995

Ruth R. Faden, Ph.D., M.P.H.
Chair
Attention: Denise Holmes
Advisory Committee on Human Radiation Experiments
1726 M. Street, N.W., Suite 600
Washington, D.C. 20036

831

Dear Dr. Faden:

Thank you for your letter of February 15. My own view of the current system of assuring the ethical conduct of medical research is that it is an excellent one. It is based at the local level. The human subjects research committees are broad-based, with representation from the community, as well as from ethicists and scientists. A very careful annual review of research projects is carried out, and the committees are kept aware of the outcome of the approved studies. Compliance with the system is outstanding, as I know of no cases where research involving human subjects does not receive prior approval from the local human subjects research committee.

In addition to these safeguards, all of the national protocols, as well as the protocols of cancer centers and protocols supported under NCI research grants, are reviewed by the granting agency and by the committees which carry out peer review of the proposals. This provides a high level of scientific, as well as ethical, review.

Evaluation of new devices is carried out under the FDA regulations which are quite stringent in terms of human subjects review and approval.

The national groups which conduct studies involving radiation in humans maintain their own strict review of compliance. Site visits are carried out regularly in which one of the major questions is - Is there a properly worded and signed consent form present in the records to document compliance with human subjects regulations?

It is my opinion that the current system is extremely effective; it is well monitored; and yet it is tolerable. The latter is the case since it is administered at the local level and by the involved sponsoring agencies and national groups, rather than by a major federal bureaucracy. I strongly support the maintenance of the current system of regulating human subjects research and the radiation research which is an integral part of this system.

Sincerely yours,

Theodore L. Phillips, M.D.
Professor and Chairman

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Ernest D. Prentice, Ph.D.
Associate Dean for Research

February 20, 1995

Ruth R. Faden, Ph.D., M.P.H.
Chair
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1726 M Street, N.W., Suite 600
Washington, D.C. 20036

Dear Dr. Faden:

Thank you for your letter of February 10, 1995 and the opportunity to offer comment on the current system for protection of the rights and welfare of human subjects. As you know, the current system of protection is primarily based upon the assumption that the Institutional Review Board (IRB) at any given institution is fulfilling their charge in an adequate manner. The IRB is not, however, a perfect system and it never will be. It is also not a comprehensive system of protection.

Currently, I think there is little doubt that a study of the IRB system would reveal the existence of inconsistency among IRBs in terms of interpretation and application of HHS (45CFR46) and FDA (21 CFR 50.56) regulations. I base this statement on 14 years of experience which has involved a great deal of interaction with IRBs across the nation. While the regulations were not written in a "black and white" inflexible fashion, if inconsistency leads to variable standards of protection, this is obviously a problem which should be corrected. In my opinion, the regulations could be revised for greater clarity and could be expanded to better accommodate specific areas of research such as acute trauma. The present regulations are, however, not the major problem. I believe the best way to ensure that an institution has an adequate IRB is through a system of regular (e.g., every 3-5 years) on-site inspections by the Office of Protection from Research Risks (OPRR).

At the present time, FDA inspects IRBs every 3-5 years at sites which conduct FDA regulated research. While these inspections are helpful and usually lead to improvement, they are not as comprehensive or educational as a site visit conducted by OPRR. Based upon my experience as a consultant to OPRR and a member of an OPRR site visit team, I recommend serious consideration be given to expanding OPRR's staff in order to develop a system of random OPRR inspections of IRBs at multiple project assurance (MPA) institutions. While such an inspection system would not cover all sites where medical research is conducted, it certainly would result in significant improvement in the quality of IRB review at major research institutions where deficiencies are identified.

It is ironic to think that the American Association for the Accreditation of Laboratory Animal Care (AAALAC) has accredited 550+ institutions and this accreditation requires submission of a detailed self-study and AAALAC site visit every 3 years. We do not, however, have a comparable system for accreditation of institutions involved in human subject research. While the MPA system provides some accountability, it is not sufficient as evidenced by the fact that OPRR currently has 100+ compliance cases which require investigation or other action. The obvious question which arises is how many other cases of noncompliance have simply not surfaced. I do not mean to suggest that humans are frequently being abused during the course of medical or behavioral science research. I don't think this is the case. I do, however, think the IRB system could be improved through the mechanism of self-studies combined with site visits and an emphasis on education.

Finally, it must be recognized that HHS and FDA regulations do not apply to all human subject research. I assume there are hospitals and small colleges or other institutions who conduct non-federally funded and non-FDA regulated research without any IRB review. As a matter of fact, in my experience, non-MPA hospitals who do have IRBs often function at a very low level of sophistication. Thus, the IRB system is not as comprehensive as it should be.

I trust these abbreviated comments will prove helpful. If I can be of further assistance, please contact me.

Sincerely,

Ernest D. Prentice, Ph.D.
Associate Dean for Research
Vice Chairman, IRB

EDP/lmc

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February 15, 1995

Ruth R. Faden, Ph.D., M.P.H.
Advisory Committee on Human Radiation Experiments
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Washington, D.C. 20036

Dear Dr. Faden:

Thank you for your letter of February 6 requesting information from chairs of IRBs about how the present system for protecting the rights of human subjects is working. I am glad to know that your committee is well along in its important task, and I (and, I am sure, other IRB chairs) appreciate your invitation to present views on the present system.

If you had asked me the same questions fifteen years ago (when I was doing research involving interviewing of voters and public officials) I would have replied that many of the rules were unreasonable and in many cases made the kinds of research my colleagues and I conducted either more difficult or, in some cases, impossible.

Happily, however, I can say that at the present time the IRB-based system is working very well. Most of the onerous early rules have been revised in ways that continue to protect the rights of human subjects but also do not severely handicap researchers. IRBs (at least those with which I am familiar) are now composed of researchers with a wide variety of special expertise, including M.D.s experienced in medical research as well as care of patients. With very few exceptions, researchers in all fields, including those using radiation in their research, are now familiar with the regulations imposed by the Common Rule, regard them as quite reasonable, and take them into full account in preparing their research protocols. Moreover, they are well aware that our IRB refuses to approve protocols that pose some danger of violating the rules, and, with rare exceptions, they are quite willing to make the changes we require.

You understand, I am sure, that our IRB, like (all? most?) other IRB's examines both new proposals (which are valid for one year only) and requests for renewal for continuing projects for another year. We do not and cannot act as "police" investigating whether the researchers are actually following the procedures we have approved. If such investigations were required, IRBs, which are composed mainly of busy mid-career teachers/researchers would clearly be inappropriate agencies for making them.

In short, I believe that the present IRB-based system is working very well--for researchers who make the proposals, for the committees that vet them, and for the people who give informed consent to be subjects.

I hope you will find these comments of some help. I wish you and your colleagues the best of luck in your difficult but important task.

Yours sincerely,

Austin Ranney

Austin Ranney
Professor Emeritus of
Political Science
Chair, CPHS

The University of Chicago
University and University Hospitals Combined Human Use of Radioisotopes and Radioactive Drug Research Committee (#67)

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March 20, 1995

Advisory Committee on Human Radiation Experiments
1726 M Street, N.W., Suite 600
Washington, D.C. 20036
Attention: Denise Holmes

Dear Ms Holmes:

Thank you for this opportunity to share our views on the methods and safeguards that have been developed over the last several decades to ensure the safety of subjects who participate in medical studies that involve low levels of radiation. Researchers at this University have a long and distinguished record in this field and have gone to considerable lengths to ensure that this research meets the highest scientific and ethical standards.

I am the chairman of the Human Use Committee for Radioisotopes, which has evolved from a committee established at the University in 1951 to review and oversee all medical studies involving radiation and human subjects. Our committee deals with all research uses of radioisotopes in humans at the University of Chicago and at the University of Chicago Medical Center. The Human Use Committee thoroughly examines every research proposal to make certain that all aspects, such as the dose and the pharmacologic activity are safe, and that the training and expertise of the researchers and the scientific design of the proposed research are optimal. The committee also makes certain that any possible risks and benefits are adequately explained to all research subjects and that clearly worded consent forms are used prior to enrolling any subjects in a study. For all of these reasons, we are confident that the current methods of assessing and communicating risks fully protect all human subjects who choose to participate in these studies.

A separate committee, the University of Chicago's Institutional Review Board, which includes physicians, scientists, ethicists and representatives from the lay community, also reviews every research protocol that involves human subjects. No research involving radioisotope use in humans may proceed without the prior approval of both oversight committees. This extensive, multi-tiered review process ensures that no participants are subjected to any unnecessary risk and that all research subjects have been fully informed of the purpose, risks and benefits of the research and have given their written and verbal consent to every aspect of their participation in the research project.

Securing fully informed consent extends beyond communicating radiation risk to healthy volunteers, who tend to be well educated and well informed and are often involved in research themselves. It must also be designed to reach out to patients who must decide whether or not to enter a clinical trial that involves radioisotopes. Although most patients quickly become knowledgeable about their illness and all available therapies, there are some who might benefit from participating in a clinical trial but who lack the educational background that enables them easily to understand the trade-offs between risks and benefits, no matter how clearly the consent forms may be worded. We make every effort to meet this challenge by spending a good deal of time with these research subjects, explaining the details to them and their families, answering their questions and guiding them to additional sources of information. Of course, this concern extends to all clinical research, not just that involving radioisotopes, but the lack of public understanding of radiation and the misleading treatment of issues of radiation safety in the popular press can confound the best efforts of physicians and researchers to explain these matters.

Finally, allow me to add that, with the proper safeguards, the thoughtful and cautious use of human subjects in research is a critical step in the development of diagnostic and therapeutic procedures. More than 10 million Americans each year undergo medical procedures that use radiation, including diagnostic X-rays, CT scans, Nuclear Medicine procedures or radiation therapy. None of the tests or treatments in common use today could have been developed without research on a limited number of human subjects.

Sincerely,

James W. Ryan M.D.
Associate Professor of Clinical Radiology and
Chairman of the Human Use Committee for Radioisotopes
University of Chicago Medical Center

UNIVERSITY of PENNSYLVANIA

Radiation Safety Office
1412 Blockley Hall
418 Service Drive
Philadelphia, PA 19104-6021
215-898-7157
Fax: 215-898-0140

MAR 20 1995

March 17, 1995

Ruth R. Faden, Ph.D.
MPH Chairperson
Advisory Committee on Human Radiation Experiments
1726 M Street, N.W., Suite 600
Washington, DC 20036

Dear Dr. Faden:

I am writing to comment on federally sponsored Research on Humans involving ionizing radiation. I have been involved with research into the use of ionizing radiation and radioactive material for the purpose of development of new diagnostic and therapeutic modalities in medicine for over 25 years. Much of that effort has involved human research subjects.

During that time period, the safeguards have, on average, improved. Specifically this includes such items as enhancing safety factors and eliminating poor design in experiments. The important task of getting human subjects to grasp the essential elements of the risks involved by their participation in a study has been made easier by the increased data available on the effects of ionizing radiation. Distilling this information into a concise format that provides sufficient information to the layman to allow evaluation of their risk and make an informed consent to participate continues to be a challenge.

At this institution we have moved away from using the numerical descriptions of risk. These numbers are calculated and are available to administrators, risk managers, referring physicians and human subjects. The principal form of risk assessment communication is carried out by using these numbers to identify typical medical procedures with comparable risks. This list is then used by the appropriate physician(s) in both the written and oral forms of the informed consent process.

This is far from a perfect system. The effectiveness varies significantly with the awareness/concern of the referring physician. It also can vary with the financial resources of the human subjects. Rather then trying to create a perfect top to bottom management, this system strives to put these research procedures on par with standard levels of care found in the practice of medicine.

There are undoubtedly improvements that can made with any of the current approaches to this issue. One item that would be particularly valuable would be the creation of some type of index. A measure of how effective a human research review process is. The desirable elements of such an index would be:

a) It should be an independent estimator.

b) It should be an unbiased estimator.

c) It should be easy to calculate.

d) It should be understandable and available to the community in which the research is being conducted.

Having an informed community knowledgeably sharing in the benefits and the costs of a particular program is one of the most powerful tools available to the regulatory process today.

Thank you for the opportunity to comment on this matter.

Sincerely,

Mark H. Selikson, Ph.D.

95-0104 LL/lr

ST. MARY'S HOSPITAL
The Regional Medical Center

DEPARTMENT OF PATHOLOGY
Aaron D. Long, M.D.
M.G. Klein, M.D.
Thomas J. Fritz, M.D.
H.S. Mooney, M.D.
Geno Saccomanno, Ph.D., M.D.

March 10, 1995

Ruth R. Faden, Ph.D., M.P.H., Chair
Advisory Committee on Human Radiation Experiments
1726 M Street, NW, Suite 600
Washington, DC 20036

Dear Doctor Faden:

This is in answer to your letter to Ms. Ruth Michels of March 7, 1995.

Since I am a pathologist, I cannot add to how radiation problems can be handled. However, I will explain how I handle an I.R.B. meeting if radiation exposures are to be evaluated under such circumstances.

Although we do not have a radiologist or radio-physicist on the I.R.B. board, if a presentation is made and I note that radiation exposure is to be considered, I invite a radiologist and our hospital radio-physicist to attend the I.R.B. meeting to help us properly evaluate the radiation exposure liabilities to both patient and hospital. I believe this is the best solution to this issue.

If you have any other questions, please call me at 303-244-2066.

Sincerely,

G Saccomanno

Geno Saccomanno, Ph.D., M.D.
I.R.B. Board Chairman

GS/hc

836

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Washington
WASHINGTON·UNIVERSITY·IN·ST·LOUIS
School of Medicine

Radioactive Drug
Research Committee

9 March 1995

Denise Holmes
Advisory Committee on Human Radiation Experiments
1726 M Street, N.W., Suite 600
Washington, DC 20036

Dear Ms. Holmes:

I am responding to the 7 March 1995 letter from Ruth Faden addressed to me as the chairman of the Radioactive Drug Research Committee at Washington University School of Medicine. I am happy to have this opportunity to comment on current practices and current regulation of research that involves exposure to ionizing radiation. My views concerning the level of regulation of research that involves radioactive drugs already have been shared with the Advisory Committee by way of my oral presentation last summer. Clearly, I am of the opinion that medical research that involves radioactive drugs is very intensively regulated, and generally is regulated at a higher level than medical research of comparable risk that does not involve such drugs.

The approach used at Washington University School of Medicine for calculating risk of ionizing radiation is via the effective dose (or effective dose equivalent). This approach will be well known to the Advisory Committee by way of the participation of my colleague, Henry Royal, M.D., in its deliberations over the past year. Similarly, I am certain that Dr. Royal has discussed with the Advisory Committee the standardized consent-form language we use at Washington University School of Medicine for communicating risk to prospective research subjects. As you probably also are aware, the approach we use gained the highest acceptance rating among IRB members in a survey study conducted by Frank P. Castronovo, Jr., Ph.D. from Harvard Medical School (Castronovo FP Jr. An Attempt to Standardize the Radiodiagnostic Risk Statement In An Institutional Review Board Consent Form. *Invest Radiol* 1993; 28:533-538).

In short, I believe that the framework of regulation of research that involves ionizing radiation provides ample protection of human research subjects.

Sincerely yours,

Barry Siegel

Barry A. Siegel, M.D.
Professor of Radiology and Medicine
Chairman, Radioactive Drug Research Committee

BAS:mtc

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February 22, 1995

Ruth R. Faden, Ph.D., M.P.H.
Chair, Advisory Committee on Human Radiation Experiments
1726 M Street, N.W., Suite 600
Washington, D.C. 20036

Dear Dr. Faden:

I just now received your letter of February 10th regarding your request for input/views on matters pertaining to human subjects research. I understand you need to receive responses by February 24th; so, I'll FAX this letter to your committee. As time is of the essence, I'm composing this response as I type along so it may seem somewhat unorganized. We are an MPA institution with rapidly growing human research interests. I would like to see a truly common rule governing all research involving humans. Based upon the total USA experience with human studies research, it would seem feasible to accomplish this. Why should we have two sets of rules (OPRR(DHHS) and FDA) with conflicting requirements regarding "emergency research" or intervention (e.g., investigational drugs) for emergency use? Why does OPRR require assurance of compliance by legally separate off-site facilities but FDA does not? If "risk" standards are to be used as the basis for determining the level of protection (informed consent) required, why aren't those standards more objectively defined and universally agreed upon? If certain enumerated research is suitable for expedited review, why would this not apply to research, not included in the list (at least not clearly included), nonethemore invasive or risky? There appears to be no organized method of credentialling for the purpose of determining suitability to become a human subjects research investigator -- should there be such a process? Having raised these questions and issues, I close and thank you for the opportunity to respond to your quest for information.

Sincerely,

Ralph W. Trottier, Ph.D., J.D.
Professor and Attorney at Law
Chairman, IRB, Morehouse School of Medicine, Atlanta, Georgia

7

BIBLIOGRAPHY OF THE NONTHERAPEUTIC STUDIES EXAMINED IN DETAIL BY THE ADVISORY COMMITTEE

As described in chapter 7 of the Advisory Committee's final report, we identified 81 radiation experiments involving children through a review of medical literature and AEC documents from the period 1944 through 1974. Because we decided to focus on nontherapeutic research involving children, only 37 of the identified experiments could potentially qualify for our detailed risk analyses. However, only 21 of these 37 experiments were conducted or supported by the federal government. The following is a bibliography of articles which describe the 21 experiments for which the Advisory Committee carried out risk analyses.

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